January 6, 2003

Dr. Richard E. Hill, Jr.
USDA-APHIS-VS-CVB
510 South 17th Street, Suite 104
Ames, IA 50010

Dear Dr. Hill:

The American Association of Avian Pathologists (AAAP) is the primary scientific organization for poultry veterinarians and poultry disease researchers in the U. S. It is recognized under the AVMA umbrella, and meets at the AVMA meeting each year. The AAAP operates with a typical committee structure, including a Biologics Committee that addresses issues of concern to the profession regarding biologics for poultry.

At the Annual Meeting in July of this year, several poultry veterinarians who are employees of integrated poultry producers approached the AAAP Biologics Committee with some concerns about the current regulations governing the production and use of autogenous vaccines. Those concerns were deemed to be a cause for action by the AAAP Biologics Committee. Subsequently, an ad hoc Autogenous Regulations Subcommittee was formed to approach CVB, with the hope that a dialogue could be opened to address these issues.

The attached document is the result of the Subcommittee's efforts. It describes our concerns in two specific areas, and attempts to provide necessary background, reasoning, and justification. The two specific areas are (1) the time limitations on the use of isolates (and the attending requirements to request extensions) and (2) the restrictions on usage only in the herd of origin (and attending requirements to request exceptions). In your considerations, we request that these concerns be addressed as separate entities, with no connection one to another.

We emphasize that practitioners and end-users initiated this initiative. It resulted from our increasing reliance on autogenous products to supplement our basic programs coupled with our commitment to operate within an autogenous regulatory framework that no longer relates to the way our integrated animal production industry functions. Despite the unnecessary logistical hurdles imposed by the regulations, we will continue utilizing autogenous vaccines because they allow us to address emerging or localized problems for which there are no commercially available products. Many of us are now using these vaccines in a truly prophylactic manner (as opposed to a reactive response), and are

attempting to mimic as closely as possible the local antigenic strains that our birds face. We are responding to the legitimate pressures to decrease our reliance on antibiotics, to improve food safety, to improve the health and welfare of our charges, and to preserve the increasingly fragile profit margins of our businesses. Autogenous vaccines are important tools in pursuing these objectives, and the present regulations are inhibiting our ability to use them in the most effective manner.

However, let it also be known that we have no intent to use autogenous vaccines as a means to circumvent the regulations for regularly licensed products. Regularly licensed vaccines are typically more economical, and will always remain our primary choice as long as their efficacy is sufficient

The attached document was prepared, for the most part, by a broiler veterinarian. The examples provided by way of explanation and justification are drawn largely from that industry. However, this document has been reviewed by layer and turkey veterinarians, and is supported by those groups, each of which could provide their own similar, but unique, examples. Attached are letters of endorsement from the Association of Veterinarians in Broiler Production (AVBP), the Association of Veterinarians in Turkey Production (AVTP), the Association of Veterinarians in Egg Production (AVEP) and the Association of Poultry Primary Breeder Veterinarians (APPBV). [Others?] Each of those letters describes the purview of their respective constituencies. There are also several letters of endorsement from individual poultry practitioners. The swine industry is rapidly becoming integrated as well, and an endorsement from that industry is attached.

We look forward to a constructive dialogue between CVB and the AAAP Biologics Committee. We stand ready to provide any further explanation or justification you may need, and would welcome the opportunity to work with you on possible solutions, whether they be amendments to the current regulation, the designation of a new class of biologicals with new regulations, or some other solution. We sincerely hope that better regulations that satisfy the agency's mandate while allowing us to meet the needs of our industries and consumers can be formulated.

Dr. Vergil S. Davis of Lasher Associates, Inc., chair of the AAAP Biologics.Committee, will serve as your contact for further discussions.

Sincerely,

John A. Smith DVM, MS, MAM
Fieldale Farms Corp.
Autogenous Regulations Subcommittee Chair

Vergil S. Davis DVM, PhD
Lasher Associates, Inc.
AAAP Biologics Committee Chair

Attachments

Poultry Industry Needs in Relation to Autogenous Biologics

The current regulations governing the production and use of autogenous vaccines (9 CFR 113.113) no longer fully meet the needs of the modern commercial poultry industry. The changes in the new VS Memorandum 800.69 (August 30, 2002) are appreciated, and are a step in the right direction. However, we feel that they do not go far enough. Commercial poultry veterinarians, who are the end users of these products, would like the opportunity to discuss with the Center for Veterinary Biologics our additional needs and concerns. Our objectives are to obtain autogenous vaccines that are pure and safe, and which allow us to meet the challenges of emerging or localized diseases, within a regulatory framework that recognizes the current structure of our industries. We have no desire to remove the protections afforded us by the current structure, which insure that the vaccines we receive are manufactured under the highest standards and are pure and safe. Neither do we desire to lessen the impetus for commercial vaccine manufacturers to produce regularly licensed vaccines for new pathogens when that course is economically warranted. This document proposes to enumerate our specific concerns and needs, as a starting point for a discussion aimed at amending the regulatory framework to better meet the needs of both the practitioners and the regulatory agency.

The need for autogenous vaccines seems to be increasing. There are three main factors driving this need, involving the pathogens, the host, and the vaccine manufacturing and regulatory structure.

1. The pathogens: Today's vertically integrated poultry business structure has resulted in dense poultry populations in many areas. These populations turn over rapidly. Many of the pathogens of concern have a demonstrated ability to mutate and drift antigenically; Infectious Bursal Disease (IBD) and Infectious Bronchitis Virus are two major examples which are germane to the discussion of autogenous vaccines. Reovirus may be another that seems to be emerging. These large, changing poultry populations probably contribute to the more rapid emergence of variant strains of these mutable viruses, driving the need for new vaccines. Widespread use of commercial vaccines applies selection pressure that encourages the survival of mutants that are different from the vaccine strains. The immense size and wide geographic distribution of the industries create the possibility for geographically localized variants as well.

2. The host: The birds themselves have been intensely selected for productive characteristics, and as a result experience considerable physiological stress associated with rapid growth. Relatively minor antigenic changes in a pathogen which, years ago, may have gone undetected, are now resulting in measurable decreases in productivity and even overt disease in these modern, rapidly growing and heavily laying birds. This has increased the need for vaccines that are more closely matched antigenically to the resident pathogen. Couple this increased sensitivity of the modern host with our efforts to decrease the use of antimicrobials, and the need for rigorous, precise prophylactic strategies is apparent. A more permissive regulatory stance allowing aggressive use of autogenous vaccines goes hand-in-hand with efforts to decrease reliance on antimicrobials. We also are striving to decrease the incidence of salmonella in our birds.

With over 1200 serovars, autogenous salmonella vaccines are critical to advancing salmonella control, especially in primary and multiplier breeders. The increased fragility of our modern birds is especially evident in breeder males, which have been selected most intensively of all. These males no longer tolerate live *P. multocida* vaccines, and so, our reliance on killed fowl cholera vaccines has increased. Furthermore, the extreme serotype specificity of killed fowl cholera vaccines has necessitated widespread use of autogenous fowl cholera vaccines for the local serotypes.

3. The vaccine industry: The commercial vaccine industry is becoming concentrated in fewer, larger businesses, and the process for regular (as opposed to "autogenous" or "conditional") licensure of a commercial vaccine is rigorous, as it should be. Unfortunately, this structure is not exceedingly nimble. The result is that it is difficult to respond quickly to a new pathogen with a regularly licensed product. The poultry vaccine business also is extremely competitive, with narrow profit margins that depend on volume for profitability. Consequently, it is not economically feasible to respond to a geographically localized pathogen with a regularly licensed product. If either a new pathogen or a geographically localized pathogen becomes permanently established and widespread, then a regularly licensed commercial product is feasible and should be required. In the meantime, autogenous vaccines are the best alternative.

We were not privy to the development of the current regulations. It would appear that they were initially devised with the cattle and possibly the swine industries and private practitioners in mind; witness the use of the word "herd" in the regulation. It would further appear that it was assumed that autogenous vaccines would be used primarily to address sudden, severe outbreaks of livestock disease, usually in a single herd or in a localized area. Once the outbreak was quelled, it apparently was assumed that the need for the vaccine should disappear. However, we no longer use autogenous vaccines solely to control sudden epornitics. Due to the changes in our industry, in our birds, and in our disease prevention priorities described previously, we now are using autogenous products in a truly prophylactic manner. We are attempting to track "less-than-serotype" changes in these mutable and emerging viruses much more closely than in the past, and prevent problems as they emerge, not after they are out of hand. Several of us are attempting to develop strategies that use commercial vaccines as the basis of our immunization programs, with additional autogenous vaccines that evolve as the pathogens evolve, literally one step behind the pathogens. We are thereby attempting to provide the most homologous protection possible, to absolutely minimize disease and our reliance on antimicrobials.

Finally, it would appear that there has been (and probably remains) a need to protect the farmer from unscrupulous veterinarians and vaccine manufacturers, to protect veterinarians from unscrupulous colleagues and manufacturers, and to prevent unscrupulous manufacturers from using the autogenous regulations to circumvent the process of obtaining full licensure for some products. These safeguards need to remain in place. However, the current structure of the poultry industries (broilers, turkeys, and layers) is such that some of these safeguards are not only no longer needed, but are actually interfering with effective use of autogenous products. We strongly believe the

regulations could be modified to allow more efficient use without compromising prudent control. In the integrated industries, the company typically owns the parent breeder birds, and retains ownership of the production progeny. Many of the companies either have veterinarians on staff who are full-time employees of the company, or employ consulting veterinarians. These veterinarians are typically poultry specialists. The birds for which they care are the property of their employer. In terms of the veterinarian-client-patient relationship, the veterinarian is an employee and a part of the client, and the patients are his employer's animals. These veterinarians are quite capable of assessing the field safety and efficacy of the vaccines they use. The tight profit margins in the poultry industries preclude the use of any product, including a vaccine, which does not appear to give a return. The prospects of a shyster foisting a worthless product on an unsuspecting or uneducated user are slim in this business. If a veterinarian employed by an integrator is using worthless vaccines, then the problem is between that veterinarian and his employer, not between the manufacturer and the integrator. Today, in most cases, an unaffiliated practitioner or a vaccine manufacturer is not approaching the owners of poultry flocks (the integrators) with an offer to make an autogenous vaccine to solve some problem. Rather, the corporate veterinarian has identified the problem, determined the need for an autogenous vaccine (or even the need to test an autogenous vaccine as a potential solution), and is approaching the manufacturer with a fairly well characterized organism in hand, asking the manufacturer to produce the vaccine for his operation. Had we the resources and time, we could theoretically produce these vaccines in our own laboratories for use in our own birds. However, we prefer to have competent, experienced manufacturers produce them under commercial manufacturing practices. We feel that the regulations should foster this relationship, not hinder it.

With this background, here are two of our major concerns:

1. The regulations require that an autogenous vaccine be used only in the herd from which the organism was isolated [9 CFR 113.113 (a) (2) and (a) (3)], and impose extensive application procedures for use in adjacent and non-adjacent herds. We understand that Veterinary Biologics has been fairly liberal in interpreting this part of the regulation in terms of commercial poultry, and appreciate that consideration. We would be much more comfortable if the special structures of the integrated industries (whether broilers, turkeys, layers, swine, or others) were to be recognized and acknowledged in the regulation, rather than depending on the understanding of future administrators. In essence, the structure of our operations makes the criteria in paragraph (a) (3) (iii) a permanent and ongoing feature. In other words, our integrated structure, by its very nature, always proves that the "epidemiology of the disease situation ... links the designated geographic areas with the herd (i.e. flock) of origin".. Our operations have a breeder department whose task is to provide a steady supply of hatching eggs to the hatchery department, whose job in turn is to provide a steady supply of baby chicks or poults to the growout department. Autogenous vaccines, being killed products, are most applicable to use in breeder birds, often for protection of the progeny. IBD vaccine administration is probably the best example of this in the broiler industry. When a breeder pullet is vaccinated during rearing, we have no idea where her chicks might go, except that it could be anywhere within the

local operation (usually referred to as a "complex"). In some of the larger companies, it is even possible that eggs could be sent to other complexes from time to time as the need arises. A problem in a few broiler flocks in our operations is likely eventually to be a widespread problem in the entire complex. Suppose that clinical findings suggest that immune suppression due to IBD is a significant factor in a respiratory disease problem in a complex, in spite of a good commercial vaccination program. A survey is performed, and through considerable effort, a variant IBD is detected in several (but not nearly all) of the broiler flocks examined. If our judgement indicates that this variant could be the source of the problem, we would like to vaccinate essentially all of our pullets with the resulting autogenous product. We want to protect the entire operation from this emerging variant. Even if we only wanted to protect future flocks on those few broiler farms where the pathogen is currently located, we would still need to vaccinate a large proportion of the pullets, to ensure that we have vaccinated progeny available for those selected farms on future random hatch days. In many cases, the most expeditious and valid field means of determining if the autogenous vaccine will solve the problem is to vaccinate the population and see if it works. If it does, considerable savings will have been realized by reducing losses that would have occurred while the vaccine was being fully tested for immunogenicity. If it does not, there will have been no harm done other than the money ill-spent on the vaccine, and informed individuals who own the birds and stand the loss from the failure made that decision. Similar scenarios exist in the turkey and layer industries. Furthermore, in those industries, the progeny themselves could conceivably be vaccinated with autogenous vaccines at a time when the exact grow-out or production destination of those poults or pullets had not been determined.

2. The regulations originally limited vaccine production to 15 months from original isolation, or 12 months from production of the first serial, whichever came first. This, in essence, required that we re-isolate the pathogen yearly, and start with a new batch of vaccine, if we desired to use an autogenous vaccine beyond the 12 or 15 months allowed in (a) (4). The regulation allowed additional serials upon presentation of supporting information to the Administrator. The new 800.69 further defines the length of such extensions to 24 months, and further specifies the needed supporting data, including a "documentation of continued involvement". Extension beyond 24 months requires antigenicity and potency tests. <u>We do not see the need for these additional safeguards</u>. If the vaccine is working, it should be difficult or impossible to re-isolate that pathogen or otherwise "document continued involvement". Does than mean the pathogen is no longer present? Not by any means. In order to continue to use the vaccine under the current guidelines, we must stop vaccinating, allow some flocks to get sick, re-isolate the pathogen, and start over. If we must wait until progeny from unvaccinated breeder flocks become sick, find the pathogen again, make a new batch, and start vaccinating pullets again, we have, in the meantime, missed protecting a large number of pullet flocks. There will now be a large number of unvaccinated hens to go through the system over the next year. Progeny from those hens on widely distributed farms may become ill for the next year. Contract growers will be impacted. Suppose that the pathogen has indeed disappeared, and the autogenous product is no longer needed. Where is the real harm in the integrated system? The company will be using a product that is no longer needed. It is the

responsibility of the veterinarian and management to either make the determination that the product is no longer needed, or accept the financial downside to continued use. There are likely no adverse effects whatsoever on the birds or farmers from continued use of the vaccine. With many of the pathogens, such as IBD, the virus does not go away, but drifts antigenically. It is unlikely that the autogenous vaccine would suddenly become worthless. Rather, it would gradually become less effective and need to be replaced or supplemented with additional antigens. If the vaccine is working, we desire to continue until it appears that it is beginning to fail, then attempt to isolate the new variant that has arisen in the face of the current generation vaccine.