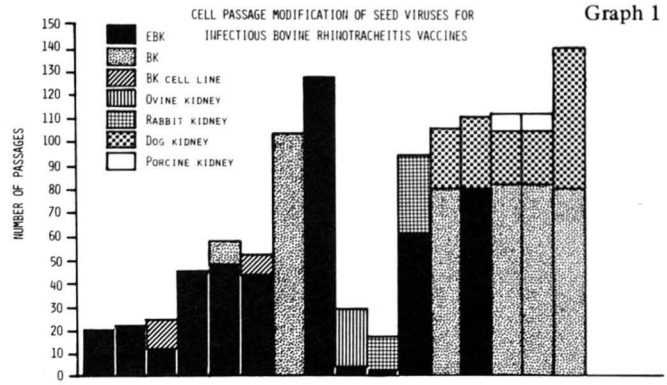
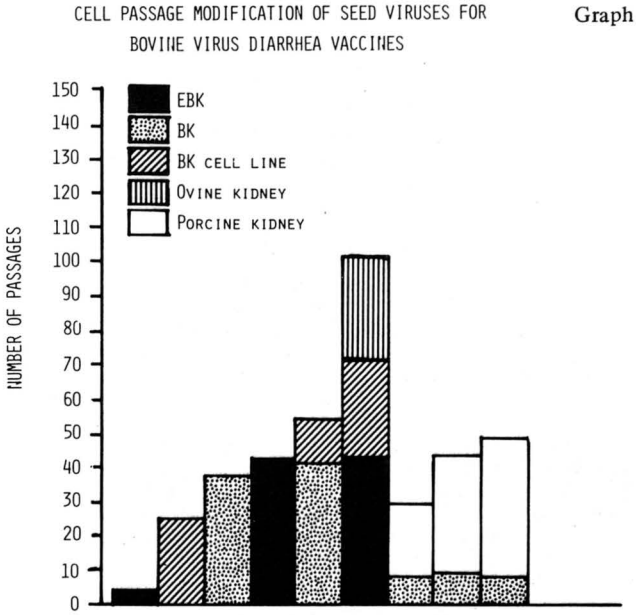
Table 6

WART VACCINES PRODUCED

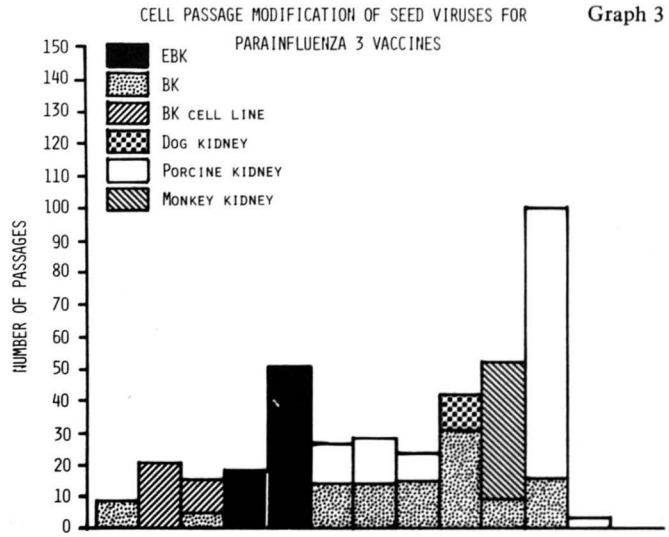
Bovine Wart Origin, Killed Virus	Ten Companies
Chick Embryo Origin, Killed Virus	Four Companies



Graph 1



Graph 2



Graph 3

Production of Biologicals Under New Government Regulations

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The Federal Government regulates the veterinary biologics industry by a law (often called the Serum-Virus-Toxin Act) enacted in March 1913. This law gives the Secretary of Agriculture authority to control the interstate movement of products for veterinary use and to insure that these products are not worthless, contaminated, dangerous, or harmful under the Act.

The Secretary of Agriculture has presently delegated the authority for biological products to the Animal and Plant Health Inspection Service. The Biologics Staff of Veterinary Services of this agency establishes conditions for licensing for both the production facility and individual products. Any person, corporate or individual, technically qualified, who can provide adequate laboratory facilities for production and testing, and with sufficient data to license at least one biological product, can become a producer of veterinary biologicals. Before you rush to Washington for a U.S. veterinary license, let us consider some of the detail that is required today in veterinary biological production.

Let us consider particularly biologicals recommended for bovine use. We divide them into three broad classes: virus vaccines, bacterial vaccines or bacterins, and antiserums and antitoxins. Important biological products to your bovine practice quickly come to mind: the vaccines for IBR, BVD, and PI_3; the clostridial bacterins, Brucella abortus vaccine, Strain 19, and *Leptospira pomona* bacterins, and antiserums against *Pasteurella sp., corynebacterium sp., E. Coli, Salmonella*, and others.

Those who are associated with the production and testing of veterinary biologicals know that this has been a changing and challenging area for many years. I consider that the year 1971 had the greatest impact upon production and testing of any in the past decade. Why? Because of government—yes. Because of industry—yes. But, more than that, I think, because man had the knowledge and capability to apply to these veterinary biologicals a greatly expanded scientific study. This extensive effort is providing products for your use that are unequaled for purity, safety, and predictable response.

To leave an impression that everything is accomplished would be wrong. There is still much to be done in the next few years. Now, for some specific examples: first—virus vaccines. Let us use IBR vaccine. This product has been used for about 20 years. It was initially developed for the concentrated feedlot problem and, to all reports, was doing a good job. Extensive competition kept the price low and it was "good insurance." This virus product, BVD, and PI_3 were recently, totally, re-evaluated by many tests called "Seed Lot Principle Testing" or "Master Seed Virus Evaluation" or similar terms. These tests are extensive and critical evaluations of the seed virus and comparable final product for identity, purity, safety, antigenicity, and immunogenicity.

1. Identity: fluorescent antibody method, serum neutralization with specific antiserum.

2. Purity: bacteriologically sterile by a sensitive test using two media and two temperatures of incubation; free from mycoplasma; free from extraneous viruses: BVD, PI_3, Reo I virus, Adeno virus I, II, III, IV; free from CPE and hemoglutinating agents.

3. Safety: ten field doses in two susceptible animals for every serial.

4. Antigenicity: serological response in 19/20 susceptible calves contrasted with five unvaccinated controls.

5. Immunogenicity: essential freedom from clinical signs after challenge in 19/20 vaccinates contrasted with five unvaccinated controls.

A lot of new information was developed. New tests and new procedures placed a technical strain upon all firms. The Biologics Laboratory furnished reagents—often several times—and developed challenge viruses and procedures for the immunogenicity test. Inventories were depleted as firms had delays or repeated the tests. Even today, industry is trying to establish normal quantities of vaccine in normal distribution channels.

Second—bacterins. Let's use two examples: *Clostridium chauvoei* products and *Leptospira pomona* bacterin. *Clostridium chauvoei* products have been with us for a long time. For many years, these products have been evaluated on a potency basis by a guinea pig vaccination-challenge test. Largely through the efforts of the Biologics Laboratory—Dr. M. E. Macheak—we know that direct correlation exists between the guinea pig protection test and cattle protection.

Thus, we have a new order of confidence in the potency of all serials marketed. With the standard spore challenge for this test supplied by government, there is assurance that all marketed products meet or exceed potency requirements. New requirements for sterility testing and for formaldehyde content also provide control upon these important elements affecting product quality.

Leptospira pomona bacterin is presently subject to extensive testing by firms and the regulatory Biologics Laboratory. Much effort has been expended by the government in an attempt to correlate cattle protection against challenge with a hamster protection test that has been used for many years. This work has been complicated by the inability to use a standard challenge culture in all hamster tests. Some have strongly suggested the need for comparisons against a reference or standard bacterin of stable potency. A provisional bacterin is now being evaluated by both government and cooperating firms.

This current situation illustrates the mixed correlation that individual firms sometimes experience with the results of the regulatory group. To my knowledge, there is no single element in error. In any such situation we consider many things: the product; test procedures; test reagents; animals; environment; etc. Often the product and its inherent variance is the most constant element between the test groups. With experience, cooperation, and time most test extremes disappear and firms expect good correlation between their own control department tests and that of the regulatory Biologics Laboratory.

The industry is working together to establish meaningful tests to evaluate host efficacy on several bacterial agents. We have no uniform tests for many agents: *Clostridium septicum; Clostridium sordelli, pasteurella multocida; Salmonella sp.; E. Coli; Corynebacterium sp.; Staphylococci; Streptococci.*

Definitive tests in the host need to be developed. But more important to the production of improved products, a new production procedure with all elements at a higher order of control is usually required. To select the culture that will produce a good product usually takes much experimentation. To integrate all the elements of production to a reproducible method—a method with production controls to assure acceptable product—usually demands at least a year, often several years. We can estimate the field evaluation of the experimental "improved" product in another year or two.

Now you can understand the scope of an improved mixed bacterin. Will it be capable of winning the "benefit/risk" challenge? Will it justify the time and effort required to gain product licensing?

Some firms are working in this area. We don't know what problems are ahead. There may be product discontinuance. There may be product formula changes. But we know that it will not be the same as yesterday.

Now, the last class—antiserums: This group of products supply supportive therapy and aid to health from passive antibody and serum factors obtained from donor animals given repeated injections of agents. An example is *Corynebacterium Pasteurella* antiserum from animals given repeated injections with these agents and with viruses of IBR, BVD, and PI_3. These products, generally, are preserved with phenol after pasteurization.

With new demands, these products have two major problems: first, to pass the more sensitive tests for sterility and, secondly, to achieve host efficacy. Sterility is not as easy as it might appear. Certainly processing is helpful, but the test is sensitive enough to pick up organisms in the venous blood. Handling production volumes increases the risks of potential exposure so that filtration methods are commonly used to provide a sterile product.

Efforts to achieve host efficacy are closely allied with similar agents in the bacterin group. Particularly, we must devise detection of relatively small amounts of specific antibody and correlate that with clinical response.

These serum products have new requirements for protein, globulin-albumin ratios, and preservative concentration. While we have little definitive evidence regarding the specific level required, it is believed that more uniform product will provide more uniform response.

The production of veterinary biologicals has reached a new order of complexity. This control will serve to reduce variation within a given product. It is not necessarily true that the individual bovine will respond to a more desirable degree. We can expect more production sophistication in the future. It is doubtful that combinations of antigens will expand to any significant degree since qualification and balance of combinations are made more complex and difficult. We continue to seek and achieve that which is possible.