

The Long and Winding Road: A History and Perspective of the Inspection Program **by Renee Schnurr**

“Put in a full day and work until 5:00. Take a break and eat at this good little restaurant on Main Street tonight and everything will work out fine.” John Mitzel, my first supervisor and mentor, shared these words of advice during my first solo inspection. I was nervous. I had just traveled by plane (for the second time in my life), rented a car (for the first time in my life), driven 3 hours (in the days when you actually could buy a folded paper map from a gas station before GPS) and now had to perform my first independent inspection in a day and a half instead of the three days I had planned for. John’s advice could not have been any better; I was able to perform a complete inspection, ate a wonderful meal and everything has worked out just fine these last 20 some years.

The inspection program at the Center for Veterinary Biologics (CVB) allows us to see how the veterinary biologics manufacturers comply with the regulations for the preparation, testing, labeling, and distribution of animal vaccines and diagnostic test kits. The inspectors understand why the regulations exist and the intended outcome of the regulations; to ensure pure, safe, potent, and effective veterinary biologics, the very basis of the Virus-Serum-Toxin Act.

On-site inspections have been a part of the Veterinary Biologics program since its inception in 1913. The first inspector was assigned to observe the production of hog cholera virus and serum in Chicago, Illinois in 1914. The Veterinary Biologics program began by focusing on strict federal control over vaccine production. Experienced inspectors were “on the line” in manufacturing facilities; supervising every step in the production process, including oversight for the testing of the products. At one time there were as many as 180 Federal employees engaged in “on the line” inspection of veterinary biological products here in the United States. This robust licensing and inspection “process control” strategy used for the first 50 years of the program provided a scientifically strong foundation.

As technology advanced and the use of cell culture replaced production of vaccine in animals, a need for a more scientific approach was necessary for inspections. Independent contract testing of veterinary biological products by universities indicated some of the vaccines prepared under the direct observation of federal employees were not meeting the purity and efficacy requirements. A redirection of inspections was announced in 1957. The focus switched from “on the line” observations (process control) to final product testing by the federal government (performance control).

The Veterinary Biologics program had started with a rich tradition of inspections by highly educated and dedicated veterinarians, but during 1964-1968 few on-site inspections were performed. The establishment of a Biologics laboratory in 1961 allowed the program to move forward and provide testing of veterinary biological products, pre- and post- licensing, as well as the development of improved assays and reagents used to measure the purity and effectiveness of vaccines. But visits to manufacturing facilities by USDA officials in 1967 uncovered many unacceptable practices including dirty production rooms, lack of records, and incomplete or non-existent testing of the product as

required by the regulations. Yet the product samples submitted to the Biologics laboratory still passed the performance based testing. It was apparent abuses in the system were occurring because of the lack of a federal presence at the manufacturing sites.

A diverse group of USDA officials met in 1968 to determine the next steps forward and the “in-depth” inspection was born. For nearly 50 years in our 100 year history, CVB has been applying a combination of performance based and process control programs to ensure manufacturers can continue to be entrepreneurs and provide the vaccines and tools needed to protect livestock, wildlife, and pets from disease.

The “on line” inspectors were centralized in Ames in the 1960’s. Many of the first inspectors played a significant role in the Biologics laboratory, especially during the years when on-site inspections were few and far between. In 1973, the inspectors were relocated to Federal Area offices at six locations across the United States to be closer to the manufacturers and to train new personnel as inspectors. The biologics laboratory merged with the National Animal Disease Diagnostic Laboratory to form the National Veterinary Services Laboratories (NVSL) in 1977.

By 1980, due to retirements and the inability to find inspectors with the advanced knowledge in the new technology involved in manufacturing and testing veterinary products, the inspection personnel were consolidated in two VS Federal Regional Offices at Scotia, New York, and Englewood, Colorado, to provide better coordination and training. In 1985, the inspectors returned to Ames, Iowa, to co-locate with their colleagues at the NVSL. Up to this point inspections had always been conducted by veterinarians supported by lay personnel trained in investigation. In Ames, the inspection staff was soon diversified to include microbiologists, epidemiologists, quality assurance, and specialists from a “new” discipline that was emerging - information technology. The integration of other disciplines in conjunction with veterinarians has generated a tradition of awareness regarding the manufacture and use of veterinary biologics that is unequaled in the world. Not only do we analyze how deviations to the production process may impact a specific antigen being made, we also realize these deviations may greatly change how the final product will perform in the animal or laboratory, in the case of diagnostic products. The scientific foundation in which the Veterinary Biologics program was built has been enhanced by the range of backgrounds found in the Inspection and Compliance group (formerly the Veterinary Biologics Field Operations) for almost 30 years.

In-depth inspections for CVB have never been about checking a box or prescribing a specific method to prepare product. It is about understanding the processes used and asking how the processes are in compliance with the regulations, so the products on the market are pure, safe, potent, and effective. It is reviewing the systems in place and competency of the men and women preparing the vaccine. Why do you do that? How do you know? What did you do? Who did that? Where was it done? The inspection process is one of trust, but verify. We understand why the manufacturers implement systems and their intent to comply with the regulations. We look for gaps in the systems and processes, and provide opportunities that allow the firms to be in compliance with the regulations. At the end of the day, both the manufacturer and CVB are striving for the same outcome, the best product on the market.

One very important feature of the inspection process (and the veterinary biologics program at large) is the dedication to compliance through education. Our actions and interactions during an in-depth inspection create an atmosphere of trust at most manufacturing sites. This trust is used to work through compliance issues in a manner that best suits the manufacturer as well as protecting the end user of the products.

Early in my career, during one inspection, we were viewing a hand-fill of killed virus product through a large viewing window. It was alarming how sloppy the technicians were; the vials were not filled uniformly and there was vaccine spilled in the hood and on the floor. As I observed, I thought, “This is why there is a requirement to check the fill volumes during a fill. When they check the fill volume they will realize how sloppy they are and correct it.” So I watched and waited, trying not to smile at the ingenuity of our perfectly formed regulations. A voice in the fill room cried out, “Fill Check!” The technicians stopped their conversation; they focused on the filling of the vials and measured the vials they had just carefully filled. Concurrent and “factual” recordkeeping was noted, the fill check was within the range required. Then the chaos of the fill resumed. It was clear that the letter of the law was followed, but the intent of the law was disregarded or, at worst, the reason for the regulation was not communicated to the technicians performing the fill.

The Inspection Team Leader (now Director of the Center) looked at me and smiled at my worried face. As carts of filled product were moved from the fill room to the hallway where we were observing, he plucked a few vials off the cart and placed them on the ledge of the observation window. He just kept pulling filled vials from the cart and placing them on the ledge. The inconsistency of the filled product was obvious as the level of pink liquid varied greatly from vial to vial. The technicians in the fill room looked at what the inspector was doing; they stopped filling and I could see right then they finally understood the grave impact they had on the vaccine and, ultimately, how it could adversely affect their company. The liaison simply said, “Yes, you’re right, we need to have a tighter control of the filling process. It is obvious that some of these vials would not meet the fill requirements noted in the outline. We will do 100% review of all the vials filled and discard the vials that do not meet the correct fill volume.”

There were no harsh words (actually no words at all), no disapproving looks; there was just an observation of an actual process in such a way the manufacturer realized the lack of control and why the process could render the vaccine worthless.

The Inspection and Compliance group continues to do unannounced inspections of commercial manufacturing and testing facilities. This process has transitioned and grown to include an emphasis on the establishment of independent quality assurance departments at each manufacturing site. In addition to reviewing actual processes and controls, our inspectors become regulatory mentors and coaches to the manufacturer’s quality assurance personnel.

When non-compliances with Federal rules and regulations are found, they are evaluated to determine the effect on the final product and appropriate action is taken. Compliance plans are put in place and

monitored by inspection personnel. Rare violations of the law that adversely affect the purity, potency, safety, or effectiveness of the product are dealt with swiftly to protect the consumer.

Being an inspector is a vocation that allows you to make a difference, to understand the impact of decisions made for scientific and business reasons, and to positively influence the direction of veterinary biologics. Growing up on a small Iowa farm that had 20-30 head of beef cattle, I have seen first-hand the impact of using safe and effective vaccines. The safeguards provided by the CVB ensure farmers, ranchers, pet owners, and small business owners (the veterinarian) can have confidence in the products they use. I am proud to be a part of the system that oversees the implementation of the Virus-Serum-Toxin Act.

I would like to acknowledge the contributions of Dr. Donald C. Randall to this article. He was able to provide integral information regarding the history of the inspection program and he is also considered the architect of the in-depth inspection process that is still in use today. Currently, Dr. Randall is the only surviving inspector who has been with the veterinary biologics program from the time of “on-line” inspections through the implementation of the current inspection process.