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National Veterinary Services Laboratories (NVSL Ames Campus) and Center for Veterinary Biologics (CVB) Laboratory Process Review

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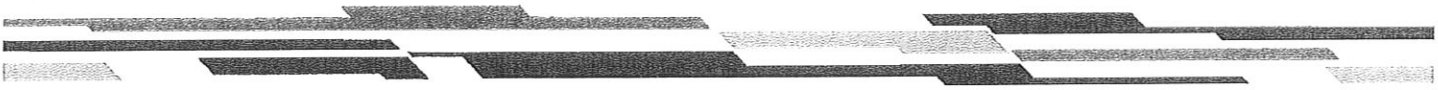

Executive Summary

The U.S. Department of Agriculture (USDA), determined there was a need to conduct an independent assessment of the technical and business operations of the Veterinary Services laboratories of the Animal and Plant Health Inspection Services (APHIS), specifically the National Veterinary Services Laboratories (NVSL) and the Center for Veterinary Biologics (CVB). The assessment by an independent consultant group was performed to provide a confirmatory review that the laboratories are taking all necessary actions to conduct their operations under a Quality Management System (QMS) with a constant goal of improving the technical execution of their missions to meet the demands of the nation's animal health industry.

The Assessment Team was provided 14 researchable questions covering a number of issues important to NVSL and CVB. They were specifically asked to determine whether there was any reason to doubt the testing procedures or results of CVB to confirm the purity, safety, potency, or efficacy of veterinary biologics in fulfillment of their regulatory responsibilities under the Virus-Serum-Toxin Act. Further, the Team was asked to determine if there was reason to doubt the results of any diagnostic testing or the results of any chemistry, pathology, or pathobiology examination or analysis done at NVSL or to be unsure of the quality of diagnostic reagents produced at the NVSL. The Team was asked to determine whether there was any reason to doubt the proper handling of Select Agents at the NVSL or CVB and if the checks and balances in place for the laboratory and technical processes appeared to be sufficient to detect or prevent problems in the areas of safety and security.

Both NVSL and CVB have embarked on an aggressive Quality Management Program with both organizations making a strategic commitment to achieve and maintain Certification to the International Organization for Standardization (ISO) 9001 and/or ISO 17025 standards. Specifically, the Assessment Team was asked how ISO Certification of NVSL's or CVB's processes for laboratory testing, inspection, licensing, or compliance activities protect the organizations or the Agency.

Finally, the Team was asked whether there any reason to doubt proper handling of confidential business information submitted to the CVB by veterinary biologics manufacturers or permittees, to have uncertainty about the quality and results of inspections and proficiency testing of National Animal Health Laboratory Network (NAHLN) laboratories, or to doubt the effectiveness of surveillance for adverse events associated with animal vaccines and other immunobiologics under the CVB Pharmacovigilance Program.

Methodology

Upon award of USDA/APHIS contract, Battelle Memorial Institute (Battelle) assembled a team of veterinary and quality assurance (QA) experts highly experienced in laboratory management. The team requested additional read-ahead documents from NVSL and CVB beyond those mentioned in the Government RFP and the Battelle proposal. A kick-off meeting was held Washington D.C. in order to finalize the Team's understanding of USDA's expectations of this review and to clarify roles, responsibilities, and expectations for execution of the overall project. Battelle was electronically provided the requested read-ahead documents, a volume of over 700 files. The Team reviewed these documents, to varying levels of detail, in order to familiarize themselves with NSVL and CVB operations and procedures prior to conducting a 4-day assessment of both organizations in Ames Iowa.

Following the initial in-briefing, the Team met with the Directors of NVSL and CVB who re-iterated the need to specifically review activities in the *Technical Services Section*, the *Pathology Section*, the *Chemical and Analytical Services Section*, the *Biological Materials Processing Section* of NVSL and the *Virology Section*, the *Bacteriology Section*, the *Inspection Section*, the *Compliance Section*, the *Pharmacovigilance Office*, and the *Select Agent Management Office* of CVB.

While conducted with the veracity of a QA audit, the purpose of this aspect of the assessment was to determine the overall effectiveness of the NVSL and CVB Quality Management Programs with a constant focus on the 14 researchable questions posed by USDA/APHIS. It should be noted that the entire NVSL/CVB staff was enormously helpful, cooperative, and patient with the Team's numerous requests for laboratory tours, explanations, interviews, data, and documentation. The on-site phase of the review culminated with an overview out-brief to the USDA/APHIS team.

Results

In reviewing activities of NVSL and CVB for the period encompassing 2003 to 2008, there were no major findings in responses to the 14 researchable questions. Because these questions were highly inter-related, the Team did not address them individually, but rather, cross-referenced the question numbers in the context of describing the major functional areas of the report, derived from the questions and guidance during the in-brief.

Issues/Observations

There were four areas where the Assessment Team felt there was some room for process improvement. These included the choice of ISO 9001 versus 17025 for some activities, suggestions to simplify the Select Agent registration process, the need for a more organized laboratory Biosafety program (in addition to the Select Agent program), and a recommendation to centralize the laboratory's training records. These four Minor Observations are discussed further below and in the body of the Report.

Quality Management Systems/ISO Certification

The NVSL and the CVB operate under quality management systems (QMS) driven through ISO standards for 17025 (NVSL) and 9001 (CVB). The operations are compliant with those standards and are improving the day-to-day operations. The management teams for both organizations take seriously the quality of their operations and have advanced these operations considerably over the last few years. The Team noted, and made recommendations to the NVSL and CVB Directors, regarding the significant differences between ISO 9001 and 17025. Specifically, whereas ISO 9001 is an overarching quality system suitable to most any laboratory setting, ISO 17025 is focused at the methodology level of detail. ISO 17025 has the greatest value when various assays or analytical methods need to be standardized, validated, and then executed in a like manner in several different facilities. Many of the diagnostic assays and procedures routinely employed by the NVSL fall into this category. In light of NVSL's global role as a reference laboratory, ISO 17025 certification of these assays represents a significant added value to their overall QMS program.

The CVB has also expressed an interest in pursuing ISO 17025 certification, but from the Team's perspective their laboratory studies appear to rely on duplication of the various manufacturers test outlines with the assay procedures differing from one product to another. Under these circumstances it would appear that there is less "value" to be derived from the effort needed to certify these tests under ISO 17025, and we suggest that adherence to ISO 9001 standards across the laboratory is sufficient. In either case, ISO Certification (ISO 9001/17025) does not "protect" the Agency in any direct manner. The commitment to, and documentation of, NVSL's and CVB's Quality Management Programs does, however, establish the basis and framework for rapid identification of quality/process problems and identification of corrective actions. It is thus more appropriately seen as a customer relations tool demonstrating that these quality programs have the same degree of external scrutiny as other laboratories in the global veterinary community.

Select Agent Certification and Procedures

A review of Select Agent Program and procedures demonstrated a well-documented and thorough understanding of Centers for Disease Control and Prevention (CDC) and APHIS regulations supported by numerous, nested standard operating procedures (SOPs). Individuals working with Select Agents were very cognizant of their responsibilities and the need for security and inventory controls. There were, however, inconsistencies noted in the type, nature, and completeness of SOPs located in each laboratory. We recommend that Select Agent Manuals be standardized across the NVSL/CVB organization to ensure accuracy, consistency, and ease of staff reference and familiarization. We also *strongly* recommend that many of the safety aspects of the Select Agent Program be extended to other infectious or potentially hazardous biological materials in the laboratories, not just the Select Agents.

The Select Agent Program was well-run but extremely complex. The Select Agents at NVSL and CVB are registered with APHIS, while those at National Animal Disease Center (NADC) are registered with the CDC. In addition, the large number of Principal Investigators (P.Is) on the NVSL/CVB registrations complicates the necessary administrative oversight. We recommend

that the Select Agent registrations be consolidated under the same oversight authority (either APHIS or CDC) and, where practical, the number of P.I.'s for the NVSL/CVB be decreased. Access to the Select Agent Program documents could also be improved through some physical consolidation. A central repository for all Select Agent records instead of [redacted] would improve document control and simplify the entire process of document retrieval.

Laboratory Biosafety

The Assessment Team noted that in the process of complying with changes in the safety, security, documentation and handling procedures for CDC/APHIS regulated Select Agents and Toxins, NVSL and CVB laboratory staff have not kept pace with accepted standards for handling of other infectious agents, at least from the standpoint of comparable documented procedures. The composition of the Select Agent lists was driven from a security perspective (e.g. the likelihood that someone could use a particular infectious agent or toxin with malicious intent) not with a view towards laboratory safety. With regards generalized Biosafety, all infectious agents and toxins should be handled in a comparable manner, in keeping with guidance found in the 5th Edition of *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* published by CDC and we recommend that NVSL/CDC SOPs should be amended or developed accordingly. Many of the SOP's and procedures developed successfully and implemented in compliance with the Select Agent rules, would be equally beneficial to generalized Biosafety practices.

We further recommend that the National Centers for Animal Health (NCAH) task their Institutional Biosafety Committee (IBC) or, preferably, a separate Biosafety Committee with the primary purpose of ensuring a robust Biosafety program based on the guidance in the BMBL dealing with all microbiological agents and toxins as the primary purpose of the committee. The committee should approve all accessions of new agents, and provide approval for all protocols involving substantial, as defined by the Committee, changes in laboratory procedures. Compliance with the Select Agent Regulations should then be a subtask of the Biosafety Committee.

Training Documentation

Accurate and well-documented training is the cornerstone to effective laboratory operations; particularly with integration of standardized quality processes such as ISO certification and highly regulated activities such as Biosafety and Select Agent use. The lack of a standardized and centralized training documentation system made it difficult for the Assessment Team to get a clear snapshot of any one individual's training status and most importantly whether or not they had completed, and were current, on specific mandatory training. It is clear that both NVSL and CVB are in the process of moving from paper to electronic systems. We recommend that any residual paper training records in the laboratories be updated to reflect a change to computerized documentation, rather than simply ending on dates that give the appearance of being in arrears.

Conclusion

In summary, we assessed both NVSL and CVB as highly efficient, well-managed organizations with a clear perspective of quality programs and customer satisfaction. There were no major Findings noted during this assessment. In deriving an overall assessment of NVSL and CVB, Dr. Norm Willis (based upon extensive personal experience and familiarity with both organizations) assisted the Battelle Team in formulating its own questions regarding the soundness of these organizations. Our answers to those questions are provided below.

1. Is there any deficiency in the current delivery of diagnostic programs?

   Currently the diagnostic programs of the NVSL do not display any deficiencies, but they are at the limit of their capacity. The ability to respond to emergency or exceptional demands may be compromised. Time available for diagnostic assay development and international reference functions are also significantly limited. The National Animal Health Laboratory Network is working well and offers access to effective surge capacity. The programs for licensing, inspection, and compliance of the CVB appear to be well and competently delivered. Staff vacancies are however, forcing consideration of a more risk-based evaluation of biologic products.

2. Is there any vulnerability that could lead to a deficiency in the diagnostic program delivery?

   Due to the required and justified emphasis on the Quality Management and Safety/Security programs in both CVB and NVSL, implementation has been at the expense of reallocating resources from diagnostic programs. This has led to the potential vulnerability of eroding capacity for emergency response.

3. How effective is the interactive relationship between the NVSL and CVB Directors and the delivery of Combined Services?

   The interactive relationship between the Directors of the CVB and NVSL is collegial and effective. Transition to the new Centers of Animal Health facility will bring about an additional resource demand.

Full Report

Introduction

The U.S. Department of Agriculture (USDA), determined there was a need to conduct an independent assessment of the technical and business operations of the Veterinary Services laboratories of the Animal and Plant Health Inspection Services (APHIS), specifically the National Veterinary Services Laboratories (NVSL) and the Center for Veterinary Biologics (CVB). The NVSL mission is to safeguard U.S. animal health by providing the nation with domestic and foreign animal disease diagnostic services, overseeing the National Animal Health Laboratory Network (NAHLN), and working closely with the World Organization for Animal Health (OIE) to provide consultation, reagents, and training for foreign countries and is recognized as Reference Laboratories for 12 bacterial and viral diseases. Also, together with the CVB and the Institute for International Cooperation in Animal Biologics of Iowa State University, is recognized as the OIE Collaborating Centre for the Diagnosis of Animal Diseases and Vaccine Evaluation in the Americas. The CVB services the nation's animal industry as the sole confirmatory and investigatory testing laboratory involved in regulation and licensing of commercial veterinary biologics (vaccines, biologics for treatment and diagnostics, and diagnostic kits). The mission of the CVB is to ensure veterinary biologics produced in or imported into the U.S. are pure, safe, potent, and effective. The CVB also works closely with the international community as part of the OIE-recognized Centre for the Diagnosis of Animal Diseases and Vaccine Evaluation in the Americas.

This assessment by an independent consultant group is to provide a confirmatory review to assure that the laboratories are taking all necessary actions to conduct their operations under a quality management system with a constant goal of improving the technical execution to meet the demands of the nation's animal health industry. The independent assessment was contracted to Battelle Memorial Institute, a not-for-profit research organization which is known for high quality technical and regulatory compliant laboratory operations and which routinely conducts inspections and audits of vendor laboratory operations for its own research requirements.

Methods and Goals

The contract to conduct the assessment was in response to a Request for Proposal (RFQ AG-63395-S-09-0019) which Battelle responded to on 14 November 2008. A contract was awarded (order number AG-6395-D-09-0112) on 21 November 2008 and work began on the effort on 24 November 2008. To initiate the contract effort a kick-off meeting was held on 4 December 2008 in Washington, D.C. The meeting was hosted by the Associate Deputy Administrator, Veterinary Services, USDA/APHIS. The purpose of the meeting was to finalize the Battelle team's understanding of the circumstances leading to the USDA's desire for an assessment, scope of the review, provide information on the laboratory operations, and provide additional guidance on how USDA desired the assessment to be conducted. At the meeting, USDA provided documentation on the laboratory operations via a DVD-ROM and discussed details of the on-site component of the assessment. The Team reviewed these documents, to varying levels

of detail, in order to familiarize themselves with NSVL and CVB operations and procedures prior to conducting a 4-day assessment of both organizations in Ames Iowa.

Battelle undertook the assessment by:

- Forming an experienced team of laboratory operations specialists, veterinary services experts (to include subcontract support), select agent program management, and quality assurance/quality management experts;
- Requesting and reviewing laboratory operations;
- Conducting a site visit at the laboratory operations in Ames, Iowa;
- During the on-site activities, interviewing personnel, reviewing additional documentation, and auditing specific products;
- Interpreting the materials/interviews to formulate an assessment by compiling the findings of the documents, interviews, lab inspections and holding team discussions on the data; and
- Garnering USDA input during the assessment through phone conferences and meetings.

Based on the Request for Proposal (RFP) and the kick-off meeting, Battelle identified five primary assessment goals:

- Become familiar with NVSL and CVB organization, processes, and procedures through read-ahead materials and the Ames site visit
- Focus assessment and review activities on specific organizational components of NVSL and CVB as identified by their respective Directors
- Evaluate the effectiveness and impact of ISO 17025 and 9001 registration on technical and business operations
- Evaluate overall select agent Biosafety and security practices of NVSL and CVB
- Answer 14 researchable Questions posed in the RFP, specifically:

    1. For January 2003 – present, is there reason to doubt the testing procedures or results done by CVB to confirm the purity, safety, potency, or efficacy of veterinary biologics?
    2. For January 2003 – present, is there reason to doubt the proper handling of Select Agents at the CVB?
    3. Do the checks and balances in place for the laboratory and other technical processes, and for safety and security issues, appear to be sufficient to detect/prevent problems in those areas?
    4. Are the technical processes and safety/security functions working properly?
    5. For January 2003 – present, is there reason to doubt regulatory decisions made under the Virus-Serum-Toxin Act?
    6. For January 2003 – present, is there reason to doubt proper handling of confidential business information submitted to the CVB by veterinary biologics manufacturers or permittees?
    7. How does ISO Certification of CVB's processes for laboratory testing, inspection, licensing, or compliance activities protect the Agency?
    8. Is there any reason to doubt the effectiveness of surveillance for adverse events associated with animal vaccines and other immunobiologics under the CVB Pharmacovigilance Program?
    9. How does an ISO Certification of NVSL process protect the Agency?

10. For January 2003 – present, is there reason to doubt the results of any diagnostic testing done at the NVSL in Ames?
11. For January 2003 – present, is there any reason to doubt the results of any chemistry, pathology, or pathobiology examination or analysis done at the NVSL?
12. For January 2003 – present, is there any reason to have uncertainty about the proper handling and use of Select Agents at the NVSL in Ames?
13. For 2003 – present, is there any reason to have uncertainty about the quality and results of inspections and proficiency testing of NAHLN laboratories?
14. For January 2003 – present, is there any reason to be unsure of the quality of diagnostic reagents produced at the NVSL?

Because these questions were highly inter-related, the Team did not address them individually, but rather, cross-referenced the question numbers in the context of describing the major functional areas of the report, derived from the questions and guidance during the in-brief.

Assessment Findings and Recommendations

Laboratory Quality Management Systems (ISO Systems 17025 and 9001)

Issue (Questions 4, 7 and 9)

Since 2003, both NVSL and CVB have embarked on an aggressive Quality Management Program with both organizations making a strategic commitment of Certification to ISO 9001 and/or ISO 17025 standards. Five years into this endeavor, Battelle was asked to evaluate and interpret how ISO Certification of NVSL's or CVB's processes for laboratory testing, inspection, licensing, or compliance activities protects the organizations or the Agency.

Observations:

The NVSL and CVB operate under quality management systems (QMS) driven through ISO standards for 17025 (NVSL) and 9001 (CVB). The operations are compliant with those standards and are improving the day-to-day operations in an effort to continuously improve the overall mission accomplishments. The management teams for both organizations take seriously the quality of their operations and have advanced these operations considerably over the last few years.

Evaluation of the implementation of the QMS was conducted through document review, interview of technical staff and management, and review of laboratories operating under the systems as well as some that do not.

The NVSL operates under ISO 17025 Accreditation starting in 2006 and CVB under ISO 9001 Certification starting in 2007. The operations that are covered by the systems are well defined and the implementation clearly outlined in the Quality Manuals for the two laboratories. The staff has received base-line training on the systems and management is well versed and supportive of operating under ISO requirements. In all the laboratories visited the operations were observed to be executed under standardized methods and procedures (SOPs, approved methods, accepted operating parameters, such as containment labs entry/exit procedures, select agent control and use documentation procedures). Personnel, both management and technical

staff, knew the requirements for using document-controlled procedures, training and proficiency testing (where appropriate) on the procedures prior to conducting testing, and maintaining good documentation of what operations had been and were being performed. The staff seems accepting of the more stringent control of procedures and processes and was actively striving to be compliant with the quality system demands. Most equipment requiring certification or recertification was being properly certified. The elements of the ISO systems, both 17025 and 9001, were being accomplished. The internal/self-auditing requirements are being completed by staff members volunteering for the role that are then trained by Quality Assurance (QA) staff to serve as internal auditors. The Management Review that was observed was a very thorough process with engaged management and QA staff. It was stated that all staff (technical management and support) have quality objectives in their performance goals. The corrective and preventive action process is effectively tracking individual events, and is maturing towards a system capable of identifying them as interrelated and often dependent components.

In order to assess the quality of and compliance to ISO 17025 with respect to sample handling, diagnostic testing, data processing, results reporting, quality of reagents and equipment used, and training of staff involved, it was decided that the Assessment Team would pursue a chain-of-custody style of audit. In some instances, a specific sample was picked to trace through the system, in others, a tour of the generic path a sample would take while in a particular laboratory or testing scenario was followed.

During laboratory visits there were indications that staff members and internal auditors are not actively looking for improvement or questioning the processes and procedures. This could be demonstrated in the type of signage and procedures posted in many laboratories. It was common to see signage that was unclear, equipment records incomplete, lacking some entries, or exhibiting entry scratch-outs that were not single line strike-outs and not initialed and dated. There was a lack of expiration dates on many reagents, chemicals, or working solutions and most of the technical staff did not see this as a problem or how this could be controlled through procedural documents. Several laboratories had cluttered work spaces and hood lines. Biological Safety Cabinets were commonly shut off when not in use and there was a lack of consistency in understanding the time required for equilibration or verification that the hood was ready to be used after turning it on. In some areas there was a lack of equipment log books or logs that could not be located or possibly did not exist. There did not seem to be a uniform process for equipment installation and upkeep, but most of the broken equipment was properly labeled as out-of-service. Responsibility for the equipment and laboratory operating status was usually stated as being that of people working in the labs, but it was not always clear how this was implemented or what authority the individuals had for controlling the space processes (suite supervisors or space managers as a function does not seem to exist). Material Safety Data Sheets (MSDSs) in most labs could be pulled up on line, but in a couple of places the personnel did not seem to have a good grasp of the process. In one instance staff members were documented as being trained on an SOP that had not yet been written. The internal auditors are not catching these things or are not looking for them; suggesting that their current training and mentoring is not effective or that they do not see these types of issues as their responsibility.

Recommendations:

Overall, this quality system is functioning well, though still maturing. There is evidence that some areas of weakness are recognized and there is active participation throughout the organization with respect to improvement. Some areas of improvement were discovered during this assessment and are summarized in separate in-depth Quality Assessment reviews conducted of NVSL and CVB, which will be provided as a supplement to this report.

The Assessment Team noted, and made recommendations to the NVSL and CVB Directors, the significant differences between ISO 9001 and 17025. Specifically, whereas ISO 9001 is an "overarching" quality system suitable to most any laboratory setting, ISO 17025 is focused at the methodology level of detail. In our view, ISO 17025 has the greatest value when various assays or analytical methods need to be standardized, validated, and then executed in a like manner in several different facilities. Many of the diagnostic assays and procedures routinely employed by the NVSL fall into this category. In light of NVSL's global role as a reference laboratory, ISO 17025 certification of these assays represents a significant "added value" to their overall QMS program.

According to presentations made to the Assessment Team, the CVB has also expressed an interest in pursuing ISO 17025 certification, but from our perspective their laboratory studies appear to rely on duplication of the various respective manufacturers test outlines with the assay procedures differing from one product to another. Under these circumstances it would appear that there is less "value" to be derived from the effort needed to certify these tests under ISO 17025, and we suggest that adherence to ISO 9001 standards across the laboratory is sufficient.

In either case, ISO Certification (ISO 9001/17025) does not "protect" the Agency in any direct manner, per se. The commitment to, and documentation of, NVSL's and CVB's Quality Management Programs does, however, establish the basis and framework for rapid identification of quality/process problems and identification of corrective actions. It is thus more appropriately seen as a 'customer relations' tool demonstrating that these quality programs have the same degree of external scrutiny as other laboratories in the global veterinary community.

Select Agent Program

Issue: (Questions 2, 3, 4 and 12)

The Team was asked to determine whether there was any reason to doubt the proper handling of Select Agents at the NVSL or CVB and if the checks and balances in place for the laboratory and other technical processes, and for safety and security issues, appeared to be sufficient to detect/prevent problems in those areas and if the technical processes and safety/security functions were working properly.

Observations:

NVSL and CVB filed a combined Registration with APHIS in March 2003, were granted Provisional Registration in 2005, and obtained their final Certificate of Registration in March, 2008. The CVB Director is the Responsible Official (R.O.), with 4 Alternate Responsible Officials (A.R.O.).

[redacted]

This Select Agent Registration is somewhat unique in that, in addition to reference biological Select Agents, a majority of the laboratories holdings derive from clinical samples submitted from the field which are declared on *APHIS/CDC Form 4 – Report of Identification of a Select Agent or Toxin in a Clinical or Diagnostic Laboratory* with the purpose of "Registration to Maintain." There is very little activity in either NVSL or CVB requiring documentation on *APHIS/CDC Form 2 - Request to Transfer Select Agents and Toxins*. For 2008, for example, there were no Receipts, 5 Transfers, and over 90 Identifications. The greatest challenge to the P.I.s appears to be *when* to report definitive isolation and the decision to maintain the isolate in the collection for reference purposes. There have also been several instances where a P.I.'s Registration needed to be hastily amended to account for isolation of a Select Agent in their respective laboratory that they were not previously approved to handle or store – another reason to consider migrating from a P.I.-based registration to an overarching laboratory registration if acceptable to APHIS.

A review of Select Agent Program documents demonstrated a well-documented and thorough understanding of CDC/APHIS regulations supported by numerous, nested SOPs. [redacted]

[redacted]

[redacted] The first-generation Select Agent database was developed in-house with inventory now being migrated to the [redacted]

(b)(3) [redacted]

[redacted] There were several notable instances of inventory discrepancies in the 2005/2006 timeframe, however it appears that more recent control measures have all but eliminated such inconsistencies. The current Select Agent policy calls for immediate discrepancy reporting – with "immediate" defined as within 24 hours. The philosophy of *"it's still Reportable even if you find it"* is commendable. [redacted]

The Select Agent Program was also examined by using a Chain of Custody tracking method. A [redacted] stock received from an outside source in June 2007 was tracked from receipt to present. The documents examined in relation to this stock were:

- The CDC/APHIS Form 2 (transfer approval),
- Chain of Custody form,
- Select agent and LIMS training records and Department of Justice (DoJ) approvals for all staff associated with transactions for this agent,
- Entries in the inventory database, and
- Section 4A of the entity's APHIS registration [redacted]

Both initial and refresher Select Agent training slides and associated quizzes were examined onsite and found to be quite comprehensive and well organized. The training also included a substantial amount of Biosafety training, which was reassuring since the team found no other evidence of a structured comprehensive Biosafety training program.

Great care is taken to secure the Select Agent Program documents that are kept [redacted]

Recommendations:

As previously stated, Select Agent documentation was very good. There were, however, inconsistencies in the type, nature, and completeness of SOPs located in each laboratory. This was most apparent in the NVSL Diagnostic Virology BSL-3 laboratory where the respective Select Agent Manuals, while conspicuously present in all three sections (Avian, Bovine/Porcine, and Equine/Ovine), each had different content and organization. We recommend that Select Agent Manuals be standardized across the NVSL/CVB organization (at the discretion of the Select Agent Manager and staff rather than the individual P.I.s) to ensure accuracy, consistency, and ease of staff reference and familiarization. We also *strongly* recommend that many of the safety aspects of the Select Agent Program be extended to other biological materials in the laboratories (see the discussion/recommendations regarding general Biosafety below).

The Select Agent Program was well-run but extremely complex. The Select Agents at NVSL and CVB are registered with APHIS, while those at NADC are registered with CDC. In addition, there are a large number of P.I.'s on the NVSL/CVB registration, further complicating the registration. We recommend upon moving to the new building the registrations be under the same authority (either APHIS or CDC) and the number of P.I.'s for the NVSL/CVB be decreased. The Select Agent Program documents could also be improved through some physical consolidation. A central place for all select agent records to reside instead of [redacted] would improve document control and simplify the entire process of document retrieval.

[redacted]

Laboratory Biosafety

Issue: (Questions 1, 2, 3, 4 and 6)

It was noted during our Assessment that NVSL and CVB staff members appear to make a clear mental (and procedural) distinction between Select Agents and "other" microbiological agents and toxins.

Observations:

[redacted]

All redactions on this page are pursuant to exemption (b)(2)(Hgh)

[redacted]

maintenance/upkeep of "Spill Kits" and "First Aid Kits" is highly variable between and within the same laboratories – checking and verifying the presences of contents, instructions and labeling is not being done in some labs and not consistent in others.

[redacted]

Recommendations:

Given the importance in the implementation of the Select Agent Program, it is recommended that the general Biosafety/Biosecurety program of the NCAH be based primarily on the following:

- Biosafety in Microbiological and Biomedical Laboratories 5th Ed (BMBL); CDC and National Institutes of Health (NIH)
- Occupational Safety and Health Administration (OSHA) Regulations; 29 Code of Federal Regulations (CFR) 1910.1200 and 1910.1450
- NIH Guidelines for Research Involving Recombinant DNA Molecules

These documents and regulations represent the requirements necessary for the safe operation of microbiology laboratories. A number of valid reasons exist for increased emphasis on the BMBL as the primary source document for the Biosafety program rather than relying exclusively on the CFRs governing the Select Agent Program.

- The Select Agent Program covers only those microorganisms and toxins with a potential to be used as biological weapons. Other microorganisms commonly occurring in animal species have produced laboratory acquired infections (LAI)
- Basing the Biosafety program on the guidance in the BMBL will allow the same biological risk assessments to be conducted on all microbiological agents and toxins brought into the laboratories, whether identified as Select Agents or not. This will provide an equal degree of rigor and a uniform guide for the selection of Biosafety levels, microbiological practices, and PPE to prevent LAI. Given NVSL's volume of unknown/suspect diagnostic samples, treating all within the framework of a common Biosafety program would greatly mitigate or preclude LAI.
- Biosafety as defined by the BMBL is a stable laboratory practice. This is not true of the laws and regulations governing biosecurity. The concept of biosecurity is truly only 7 years-old, dating from the mailing of the anthrax letters in September and October of 2001 and has been

continually evolving. Various authors have tried to separate biosecurity from Biosafety, but the BMBL contains in Section VI *Principles of Laboratory Security* the following:

"Biosafety and Biosurety programs share common components. Both are based on risk assessment and management methodology; personnel expertise and responsibility; control and accountability for research materials including microorganisms and culture stocks; access control elements, material transfer documentation, training, emergency planning, and program management."

The NVSL and the CVB are provided Biosafety and biosecurity support by the Safety and Security Unit of the National Centers for Animal Health (NCAH). The NCAH Safety and Health Council (SHC) reports directly to the NCAH Board of Directors and is responsible for promoting a strong proactive safety and health program. The draft NCAH Biosafety Manual provides the memberships and the responsibilities of the Institutional Biosafety Committees (IBC) for the NVSL and the CVB. The IBCs function to both review compliance with the *NIH Guidelines for Research Involving Recombinant DNA Molecules* and for reviewing protocols involving etiological agents. The reporting chains of the IBCs and the Institutional Animal Care and Use Committees (IACUC) are not defined in the draft Biosafety Manual. A strong, effective Biosafety program should have a direct reporting line to the NCAH Board of Directors through the NCAH SHC. This committee should provide each of the sections/units with a uniform Biosafety and Biosecurity Handbook with overarching guidance on implementation. The Biosafety and Biosecurity Handbook would cover risk assessment for each agent, a material safety data sheet, and the containment and PPE necessary for safely working with the agent. This would be the only Handbook registered with the Quality Assurance Group and would be the basis for any internal Biosafety/biosecurity inspections. Accountable supervisors would add to this only rarely and then with the approval of the Biosafety Committee. The NCAH needs uniform policies when working with each biological agent to defend the Biosafety program to external scientific, regulatory and political groups.

We recommend that the NCAH task the IBC or, preferably, a separate Biosafety Committee with the primary purpose of ensuring a robust Biosafety program based on the guidance in the BMBL dealing with all microbiological agents and toxins as the primary purpose of the committee. The committee should approve all accessions of new agents, and provide approval for all protocols involving substantial, as defined by the Committee, changes in procedures. Compliance with the Select Agent Regulations should be a subtask of the committee.

Training Systems and Documentation

Issue: (Questions 1-14)

Accurate and well-documented training is the cornerstone to effective laboratory operations; particularly with integration of standardized quality processes such as ISO certification and highly regulated activities such as Biosafety and Select Agent use.

Observations:

The lack of a standardized and centralized training documentation system made it difficult for the Assessment Team to get a clear snapshot of any one individual's training status and most importantly whether or not they had completed, and were current in, specific mandatory training. It is clear that both NVSL and CVB are in the process of moving from paper to electronic systems. There is an obvious lack of consistency between laboratories regarding "who" is responsible for training and training documentation, how it is done and where the documentation is to be maintained. Training is being done, but virtually all records that were reviewed lacked something: e.g. 'sign-offs,' specific data entries, or linkage to the materials used for training. There also seemed to be a reliance on proficiency testing, in some laboratories as a substitute for training. Proficiency testing is not training.

Staff members receive training on a variety of topics, to include job specific, USDA required, as well as safety & security training. The CVB quality manual states that staff training is maintained in the respective labs, but also states that staff training is maintained by the director. These statements, as written, provide contradictory information. When asked to see training files for selected staff, as well as the list of required qualification (as required by the quality manual) it was clear that the system for maintaining training files is fragmented, and the process is not well defined in writing. The Team observed this issue across the entire organization during the assessment of both operations (NVSL & CVB). The Quality Manager stated that in 2006, an onsite ISO training was provided, and since then various ISO related topics have been covered.

Recommendations:

We recommend an overall review of the process of training, training documentation, and assign a responsible person as the training coordinator for all the laboratory activities or one for NVSL and one for CVB. For CVB, it is recommended that at the very least, the quality manual include one section on training, and include a complete description of the training process all in one section, including grand fathering of staff previously hired, and locations of the different training files, so as to avoid contradictory statements. This was discussed with the CVB Quality Manager. Based on this information and documentation related observations in the lab (see below) it was recommended that the CVB Quality Manager consider providing a brief ISO refresher training every 1 to 2 years, to include documentation requirements and any significant issues or findings and lessons learned.

Laboratory Security

[redacted]

Licensing and Regulatory Activities

Issue: (Questions 5, 6, and 10)

CVB regulates veterinary biologics (vaccines, bacterins, antisera, diagnostic kits, and other products of biological origin) to ensure that the veterinary biologics available for the diagnosis, prevention, and treatment of animal diseases are pure, safe, potent, and effective. This activity is in direct support of USDA/APHIS mission to uphold and enforce the provisions of the Virus-Serum-Toxin Act (21 USC 151-159 et. seq.) of 1913. Per overview briefing provided the Assessment Team, CVB is currently regulating ~2,400 products focused on diagnosis, prevention or treatment of over 111 distinct animal diseases. The regulatory process encompasses facility inspection, compliance review of licensure submissions, and laboratory confirmation of manufacturers test results. Over the past several years, CVB laboratory testing has focused more upon 'pre-license' serials, and somewhat less upon concurrent testing of retained samples.

Observations:

In the Quality Audit phase of the CVB Assessment the licensure files were reviewed for two products, chosen because their documentation spanned the period of interest (2003-2008):

- Porcine Circovirus Vaccine, Type 2, Killed Baculovirus Vector, Code 19K5.R0 (Boehringer Ingelheim Vetmedica, Intl/U.S. Veterinary License #124)
- Swine Influenza Vaccine, H1H1 and H3N2, Killed Virus, *Erysipelothrix rhusiopathiae – Mycoplasma hyopneumoniae* Bacterin
- The records overall were very thorough, meticulous, and could easily be interpreted by a reviewer with no specific background or familiarity with the product. Documented communications between CVB and Manufacturer were very similar to comparable dialogue between the FDA/CBER and human biological manufacturers. As described

and demonstrated, CVB's regulatory processes and procedures appear to be effective and efficient.

Recommendations:

The Assessment Team has no recommendations.

Pharmacovigilance Program

Issue: (Question 8)

Identification and reporting of any product discrepancies or Adverse Events associated with a product's use is a critical component of the regulatory process. The Assessment Team was asked whether there was any reason to doubt the effectiveness of surveillance for adverse events associated with animal vaccines and other immunobiologics under the CVB Pharmacovigilance Program.

It was of note that USDA's overall "Adverse Event" reporting system is voluntary and that input from the field comes to CVB both from end-users of products as well as biologics manufacturers, which were *required* to report to CVB any event reported directly to them.

Observations:

The USDA website; both via the URL provided during the Assessment visit and by following the links [APHIS Home Page >> Animal Health >> Veterinary Biologics >>Adverse Event Reporting Program] is difficult to navigate. Definitions of Adverse Events Reporting Program and how to report them is are hard to find on the APHIS website:

"An adverse event is any undesirable occurrence after the use of an immunobiological product, including illness or reaction, whether or not the event was caused by the product. For products intended to diagnose disease, adverse events refer to anything that hinders discovery of the correct diagnosis.

The mission of the USDA is to ensure that animal immunobiologics are in compliance with the Virus-Serum-Toxin Act. Reports are assessed for the possibility of a product deficiency. When necessary, testing is performed or additional information sought. The USDA is, however, unable to make diagnoses or recommendations specific to individual cases. Some of the manufacturers do provide such services. Receipt of a report by the USDA does not necessarily imply that the product caused an adverse event, or even that a particular event actually occurred."

For the period 2003-2008 a total of 2045 Adverse Event Reports were received (~350/year on average), resulting in 71 more detailed investigations. It's not altogether surprising that most of the events reported were localized or hypersensitivity type reactions, predominantly reported in companion animals. With over 2,100 active CVB-regulated products, this incidence of Adverse Event Reporting appears altogether too low. We see four possible interpretations (not mutually exclusive): a) CVB's Licensing and Regulation process is extremely effective in weeding out unsafe/reactogenic products, b) overall owner/end-user tolerance to mild-to-moderate adverse effects is sufficient to negate reporting, c) as a "voluntary" program, there is insufficient motivation/guidance regarding "how, what, and when" to report and/or d) veterinary products do not get the same scrutiny for Adverse Events as human products do.

Recommendations:

No irregularities were noted in the Pharmacovigilance program overall. The numbers of Adverse Events reported over the past five years is too low to be of any statistical significance. We believe that Adverse Event Reporting overall would be improved if it were made mandatory, at least to the level of licensed veterinarians using the products.

National Animal Health Laboratory Network

Issue: (Question 13)

The National Animal Health Laboratory Network (NAHLN) is part of a nationwide strategy to coordinate the work of laboratories providing surveillance and testing services. The NAHLN was established in 2002 to link federal diagnostic laboratories with state and university diagnostic laboratories. It has now matured into a network of 54 state and university laboratories and 4 federal laboratories located in 45 states. The primary goals of the NAHLN are:

- Provide accessible, timely, accurate, and consistent animal disease laboratory services nationwide,
- Provide laboratory data to meet epidemiological and disease-reporting needs,
- Maintain the capacity and capability to provide laboratory services in support of responses to foreign animal disease outbreaks and other adverse animal health events,
- Focus on diseases of livestock (exotic, zoonotic, and emerging diseases), while including diseases of non-livestock species.

Observations:

To meet these goals, the program has initiated national training for laboratory personnel, proficiency testing, quality assurance, upgraded facilities and exercises based on animal health emergencies to test the communications and reporting protocols in place in the network.

The NAHLN provides a rapid, reliable means to respond to animal emergencies related to the introduction of foreign animal diseases (FAD) including foot and mouth disease (FMD), exotic Newcastle disease, avian influenza and bovine spongiform encephalopathy (BSE). A primary need in case of the diagnosis of FAD in the US is the rapid assessment of the increasing numbers of samples for disease diagnosis. The NAHLN provides this capability.

Recommendations:

The NAHLN has evolved into a nationwide, quality controlled resource for rapid, diagnostic response. The implementation includes standardized techniques, training in those techniques, and proficiency testing. We found no reason to be uncertain about the quality and results of the diagnostic procedures, inspections and proficiency testing of the member laboratories.

Conclusions

Overall, we assessed both NVSL and CVB as highly efficient, well-managed organizations with a clear perspective of quality programs and 'customer' satisfaction. There were no major findings related to the 14 researchable questions posed. In deriving an overall assessment of NVSL and CVB, Dr. Norm Willis (based upon extensive personal experience and familiarity with both organizations) assisted the Battelle Team in formulating its own questions regarding the soundness of these organizations. Our answers to those questions are provided below.

1. Is there any deficiency in the current delivery of diagnostic programs?

   National Veterinary Services Laboratories (NVSL)

   - Currently, the diagnostic program does not display any deficiencies.
   - It is, however, at the limit of its capacity and therefore does not maintain any excess capacity to respond to emergencies or exceptional demands.
   - The NAHLN is excellent and is providing effective coordination to achieve surge capacity.
   - The BSE and transmissible spongiform encephalopathy (TSE) diagnostic programs appear to be effectively delivered.
   - The diagnostic programs within the Diagnostic Virology Laboratory appear to be well and effectively delivered, as do the brucellosis and mycobacterial programs.
   - The time available for diagnostic assay development and international reference would appear to be significantly limited by the day-to-day sample analysis mission. This could well lead to an erosion of the exemplary international reputation which the diagnostic programs have achieved and maintained in the past.
   - In the brucellosis and mycobacterial programs, although the facility is capable of Level 3 safety, the programs do not appear to be adequately operating at this safety level.

   Center for Veterinary Biologics (CVB)

   - The programs for licensing, inspection, and compliance appear to be well and competently delivered.
   - Vacancies within the Center, however, have led to consideration of a less comprehensive, more risk-based evaluation of biologic products. While unfortunate, and although this is a fundamental change, it may be able to be achieved without significantly increasing customer complaints.
   - Bringing the entire CVB together in the new facility should enhance program delivery with some efficiency gained.

2. Is there any vulnerability that could lead to a deficiency in diagnostic program delivery?

   - The Directors of both CVB and NVSL have placed the required emphasis on the Quality Management and Safety/Security programs in both areas. These programs are essential and deserve this emphasis. The resourcing of these programs, however, has been at the expense of reallocating resources from the diagnostic programs. This has led to the

potential vulnerability of eroding capacity for emergency response. If the diagnostic demand significantly increases, response may be compromised – there is no reserve.

- There is a potential vulnerability in the Diagnostic Virology program. To organize and accommodate the transition of diagnostic programs into the new facility, the Diagnostic Virology Laboratory Director will be assigned to manage this transition for a period of at least four months. During the transition, although the time period may not be long, a very real potential vulnerability in responding to emergency demands, exists in an area where disease outbreaks most commonly occur.

3. How effective is the interactive relationship between the NVSL and CVB Directors and the delivery of Combined Services?

   - The interactive relationship between the Directors of CVB and NVSL appears to be collegial and effective. Both address this interaction with respect and openly treat it as a priority despite the significant difference in their program areas. The cooperation appears to work well and be effective.
   - Combined Services represents a different way of working for the two Directors. With acceptance of the approach, which is evident, there is an increased efficiency. It does involve trust, which once again appears to be evident, but it also involves a cost in that adequate resourcing for some of these areas is at the expense of diagnostic or biologic program delivery. Consideration should be given to rationalizing resource allocation, particularly in the areas of quality management, safety/security, and select agents, with the requirements for an effective and comprehensive diagnostic program.
   - Transition to the new facility will be very demanding. Significant additional resources will be required to maintain the new facility. The transition of diagnostic programs will need additional resources to establish equipment and programs to the required standards in the new facility, while maintaining current program delivery.
   - The new facility will become an item of international interest and increased requests for tours will have to be managed. These requests could be substantial and should be independently resourced to avoid involving technical diagnostic staff. This could continue for a substantial period of time.

Summary

In specific response to the fourteen researchable questions initially posed by USDA, it is the Battelle Assessment Team's opinion that:

Question 1: *For January 2003 – present, is there reason to doubt the testing procedures or results done by CVB to confirm the purity, safety, potency, or efficacy of veterinary biologics?*
Response 1: No, CVB is executing a very meticulous and comprehensive program of inspection and regulation of veterinary biologics.

Question 2: *For January 2003 – present, is there reason to doubt the proper handling of Select Agents at the CVB?*
Response 2: No, Select Agents are being handled properly by CVB personnel in accordance with applicable APHIS guidance and regulations. Minor discrepancies noted are adequately documented and not atypical for a laboratory of this size and complexity. Recommendations for potential improvement are cited above.

Question 3: *Do the checks and balances in place for the laboratory and other technical processes, and for safety and security issues, appear to be sufficient to detect/prevent problems in those areas?*
Response 3: Yes, aside from minor recommendations made by the Assessment Team while on-site, the overall Select Agent Safety and overall Security programs are well-integrate and provide the necessary checks and balances to be effective.

Question 4: *Are the technical processes and safety/security functions working properly?*
Response 4: Yes, there were no significant safety or security issues noted.

Question 5: *For January 2003 – present, is there reason to doubt regulatory decisions made under the Virus-Serum-Toxin Act?*
Response 5: No, random sampling and quality review of representative documentation throughout CVB's regulatory process found no reason to doubt any historical regulatory decisions.

Question 6: *For January 2003 – present, is there reason to doubt proper handling of confidential business information submitted to the CVB by veterinary biologics manufacturers or permittees?*
Response 6: None observed as a result of this Assessment.

Question 7: *How does ISO Certification of CVB processes for laboratory testing, inspection, licensing, or compliance activities protect the Agency?*
Response 7: ISO Certification (ISO 9001/17025) does not "protect" the Agency in any direct manner, *per se*. The articulation and documentation of CVB's Quality Management Program necessary for that certification does, however, establish the basis and framework for rapid identification quality/process problems and identification of corrective actions. It is more appropriately seen as a 'customer relations' tool demonstrating that CVB, as a regulatory body, *also* undergoes external scrutiny. We recommend that CVB continue to operate under ISO 9001 and potentially reconsider the "value-added" of ISO 17025 certification.

Question 8: *Is there any reason to doubt the effectiveness of surveillance for adverse events associated with animal vaccines and other immunobiologics under the CVB Pharmacovigilance Program?*
Response 8: No, at least not within the limitations of a "voluntary" adverse event reporting process. See comments in narrative above.

Question 9: *How does an ISO Certification of NVSL process protect the Agency?*
Response 9: ISO Certification (ISO 9001/17025) does not "protect" the Agency in any direct manner, *per se.* The articulation and documentation of NVSL's Quality Management Program necessary for that certification does, however, establish the basis and framework for rapid identification quality/process problems and identification of corrective actions. It is more appropriately seen as a 'customer relations' tool demonstrating that NVSL's quality programs have the same degree of external scrutiny as other reference diagnostic laboratories in the global veterinary community. The NVSL Plan for QA (July 2003) sums this up best as *"allowing NVSL to take a leadership role through example, sharing its experience with other diagnostic laboratories for whom QA is a similar challenge."* Recommend that NVSL continue its plan for integration of methodologies into their ISO 17025 certification on a case-by-case basis.

Question 10: *For January 2003 – present, is there reason to doubt the results of any diagnostic testing done at the NVSL in Ames?*
Response10: None noted during this Assessment.

Question 11: *For January 2003 – present, is there any reason to doubt the results of any chemistry, pathology, or pathobiology examination or analysis done at the NVSL?*
Response 11: None noted during this Assessment.

Question 12: *For January 2003 – present, is there any reason to have uncertainty about the proper handling and use of Select Agents at the NVSL in Ames?*
Response 12: No, Select Agents are being handled properly by NVSL personnel in accordance with applicable APHIS guidance and regulations. Minor discrepancies noted are adequately documented and not atypical for a laboratory of this size and complexity. Recommendations for improvement are cited above.

Question 13: *For 2003 – present, is there any reason to have uncertainty about the quality and results of inspections and proficiency testing of NAHLN laboratories?*
Response 13: None noted during this Assessment.

Question 14: *For January 2003 – present, is there any reason to be unsure of the quality of diagnostic reagents produced at the NVSL?*
Response 14: None noted during this Assessment.