May 28, 2003

VETERINARY SERVICES MEMORANDUM NO. 800.205

Subject: General Licensing Considerations: Biotechnology-derived Veterinary Biologics Categories I, II, and III

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

This guideline provides information and recommendations about the submission of documents in pursuit of licensure for biotechnology-derived veterinary biological products.

I. BACKGROUND

The Center for Veterinary Biologics (CVB) is announcing the availability of three documents entitled "Summary Information Format" (SIF) for Category I, II, and III Veterinary Biologics, respectively. These documents outline important scientific questions and information that should be addressed during the preparation of a U.S. Veterinary Biological Product License Application to the United States Department of Agriculture (USDA) for new biotechnology-derived biologics. The documents are accompanied by three example SIF submissions, one for each category.

The Categories for biotechnology-derived biologics are defined as follows. Category I consists of 3 divisions, I-A, I-B-1, and I-B-2. I-A includes bacterins, killed viruses, and subunit vaccines. I-B-1 consists of monoclonal antibodies (Mab) for therapeutic or prophylactic use, and I-B-2 includes Mab and expressed proteins for use in diagnostic test kits. Category II is comprised of live gene-deleted vaccines. Category III contains live vectored vaccines.

These guidance documents represent the agency's current thinking on this topic. They do not create or confer any rights for or on any person and do not operate to bind the USDA or the public.

II. SPECIFICATIONS

The SIF documents are designed to allow both the participating firm as well as CVB to assess the risk associated with the manufacture and release of biological organisms. Specifically, information must be provided to allow communication between the participating firm and CVB to assess the risk associated with genetically modified organisms released into the environment. Licensing of biotechnology-derived veterinary biologics products begins with the submission of data from the applicant in a standard format designated as a SIF. The purpose of the SIF is twofold: to provide specific data

about the design, construction, and testing of the biological agent construct and to provide a basis for the Risk Analysis (RA).

The SIFs are separated into three basic parts: I. The Introduction (Part A and B); II. The Description of the Regulated Biological Agent (RBA) Construction (Parts A-C); and III. Biological Properties or Virulence for the Regulated Biological Agent Used for Master Seed (Parts A-G). The introduction (Part I) should clearly state the name of the participating firm plus any collaborative departments, institutions or investigators involved with the construction or testing of the organism. The introduction should include a brief statement on the objective for the use of the proposed product, including proposed modes of administration, target species, and geographical area intended for use and where genetic engineering events took place. The introduction should also include a brief statement on the proposed development of the construct and safety testing.

The Description of the RBA Construction (Part II) should provide detailed information about the documented genetic characteristics and history of the organisms used to construct the final RBA. The genotype of the expression cassettes, selectable marker cassettes, replication cassettes, and integration cassettes must be characterized as to their origin and use within the final RBA. The biological properties of each genetic cassette (such as virulence, host animal tropism, tissue tropism, horizontal gene transfer potential, and recombination potential) must be detailed. The risk-associated properties of the genetic cassettes or RBA (such as environmental distribution, geographic distribution, recommended NIH/CDC biosafety levels, and survivability in the environment) must be addressed. Part II will culminate in a description of how the Master Seed (MS) or RBA will be characterized based on the data and information provided.

Documents containing Parts I and II of the SIF should be submitted to the CVB as soon as the proposed genetically modified organism has been constructed and before the animal testing needed for licensure has begun. An early submission will allow the CVB to provide the participating firm feedback, which will be valuable in risk management during the development of the product. It is accepted that the SIF will not be complete at this time due to the need to conduct further studies according to Part III in support of licensure. It is likely that firms will need to evaluate several constructs in host animals prior to selecting the final RBA for submission as a Master Seed. For these preliminary evaluations, it is appropriate that the firm’s Institutional Biosafety Committee (IBC) review, approve, and monitor the animal studies. However, submission of the initial documents to CVB does not preclude the firm’s IBC oversight of the project throughout the development and manufacturing process.

A team composed of CVB staff with molecular biology expertise reviews Parts I and II of the SIF and, if appropriate, obtains approval from the CVB Institutional Biosafety Committee to work with the recombinant organism in the laboratory at CVB. The Master Seed is then submitted to the CVB for confirmatory testing of the identity and purity. Following Master Seed approval, the host animal test protocols are reviewed and approved, which will include recommendations as to the appropriate containment for the

host animal safety and efficacy studies. Host animal studies that are undertaken prior to CVB approval of the MS are at the firm's risk.

Part III of the SIF is designed to provide safety data related to virulence of the proposed product. These data are often not available until the firm has Master Seed and host animal protocols approved by CVB and continues development of the desired product. Because the data generated during the development phase will require introduction of the organism into animals, it is important that the design of the experimental clinical protocols be structured using the best information contributed by both the participating firm and CVB. Peer-reviewed scientific literature about the construct or similar constructs may provide adequate documentation for some considerations. Others will require testing of the specific construct. The level of documentation available impacts the Risk Analysis (RA) and provides a basis for certainty. Thus, a detailed SIF will support the documentation required prior to authorization for release of the construct in the environment. Prior to publication of a Federal Register Notice of availability of a RA and an Environmental Assessment (EA) for public comment, the SIF must be as complete as possible.

The RA begins with the Biological Risk Assessment (BA), which is reviewed by an expert panel; the panel may include academic or non-CVB federal scientists and is approved by the Section Leader of Biotechnology, Immunology, and Diagnostics. The RA and a confidential business information-deleted SIF are then made available for public comment with notification in the Federal Register. Comments are reviewed by CVB licensing staff. If a Finding of No Significant Impact (FONSI) is made and all NEPA requirements are met in the protocol, the field trial may be approved. Mitigation procedures are included in the approval, and the firm must notify CVB immediately if adverse events occur.

Once data from Part III is completed and a preliminary RA submitted, a request for permission to ship the product for field trials may be submitted. A decision to grant permission to conduct the field trial will depend on the submission of efficacy data, an approved SIF, a study protocol, results of testing of the proposed serials, experimental labels, permission from state authorities, an RA, and responses to comments received from the Federal Register Notice. The CVB may require additional safety tests prior to authorization of field trials, including evaluation of tissue or host animal tropism alterations, safety studies in non-target animal populations, overdose studies, shed and spread studies, environmental survival studies, recombination studies, or other studies as appropriate for the design of the construct and the manner in which it will be used. Field trial results are carefully evaluated for compliance with the protocol and for adverse events. The RA, which consists of the BA, risk characterization, risk mitigation, and risk communication (via the Federal Register Notice) is then finalized. Licensure may proceed if all requirements are met and no significant adverse events have been identified.

II. GLOSSARY

1.1 Category I Biological Product

A product that is biotechnology-derived and inactivated. Examples of Category I include gene-deleted bovine rhinotracheitis and pseudorabies killed virus vaccines, feline leukemia virus subunit vaccine, therapeutic canine lymphoma monoclonal antibody, and plasmid-expressed EIA virus p26 and gp45 proteins, for use in diagnostic kits.

1.2 Category II Biological Product

A product that is biotechnology-derived, gene-deleted, and live. Examples of Category II include the numerous pseudorabies virus modified live vaccines with deletions in gX (gG), gI (gE), gIII (gC), TK, inverted repeat and U_s regions.

1.3 Category III Biological Product

A product that is a biotechnology-derived, live vector for a foreign gene insert. Examples of Category III include the avian influenza H5 and Newcastle HN and F genes in the fowl pox vector, and the canine distemper F and HA and the rabies GP in the canarypox vector.

1.4 Backbone Biological Agent (BBA)

The agent from which the genetic material from a single biological agent contributes the primary genetic and biological characteristics of the Regulated Biolgical Agent, including replication and regulatory sequences.

1.5 Donor Biological Agent (DBA)

The virus, bacterium, fungus, plant tissue, or other organism that will donate DNA or gene sequence inserted into the Backbone Biological Agent. The DBA contributes sequences encoding specific antigenic characteristics to produce gene product foreign to that of the Backbone Biological Agent.

1.6 Donor DNA or gene

The nucleic acid of the Donor Biological Agent, which may be derived from a previously isolated nucleic acid, or engineered DNA segment; however, each nucleic acid of a construct that was derived from a Donor Biological Agent should be identified. Well-characterized genes or sequences need only be referenced.

1.7 Downstream sequence

The DNA sequence that exists at the termination sequence, or 3’ end, of a gene or DNA sequence.

1.8 Flanking region or flanking sequence

The sequence of DNA of the Regulated Biological Agent contiguous to the 5’ or 3’ end of the inserted DNA cassette or modified genetic sequence.

1.9 Gene or DNA cassette

Any nucleic acid sequence that can be isolated for genetic engineering purposes. It can be derived from RNA or DNA and can include sequence for regulatory genes, structural genes, or DNA sequence encoding expressed gene product(s).

1.10 Marker Gene

The nucleic acid of the Backbone Biological Agent that can be used to distinguish an attenuated and non-attenuated form of Backbone Biological Agent. The thymidine kinase gene is a marker gene since it provides a means for a tk- virus to grow in the presence of bromodeoxyuridine. Alternately, foreign marker genes that are useful for distinguising the RBA may be inserted.

1.11 Regulated Biological Agent (RBA)

The final construct used to produce a proposed or licensed biologic of a specified lot of RBA that is established as master seed (for microorganisms) or Stable Transformed Plant Stock (for plants). The RBA was previously referred to as the recipient organism with a DNA insert.

1.12 Regulatory Sequence

The nucleic acid sequences that can be identified by regulatory gene products, including: promoters, poly A addition sites, termination regions, enhancers, origins of replication, insertion sequences, transposition sequences, restriction enzyme sites and methylation sites.

1.13 Reporter Gene

A nucleic acid inserted into the Backbone Biological Agent that expresses a specific gene product. The expressed product serves as a signal or reporter molecule to signify a successful recombination event into the Backbone Biological Agent.

1.14 Upstream sequence

The DNA sequence that exists at the start site of, or 5'end of, a gene or DNA sequence.

III. COMMENTS

These documents are being distributed for implementation at this time. Interested persons may submit comments or questions regarding these guidance documents to Louise M. Henderson, Ph.D., at the Center for Veterinary Biologics.

IV. ELECTRONIC ACCESS

Persons with access to the Internet may obtain the documents at the following location: http://www.aphis.usda.gov/vs/cvb

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