Summary Information Format Category IV: Production Platform for Veterinary Biologics

I. Introduction

Biotechnology-derived biologics can be generated by the repeated use of the same production system, creating new products with just the replacement of an inserted gene or set of genes. Examples include, but are not limited to, virus vectors containing a transgene, bacterial/plasmid vector or eukaryotic cell line expression systems expressing a subunit protein, and virus-like particles containing a nucleic acid insert. These expression systems are referred to as Production Platforms. As an alternative to full testing of each new construct within an agent-specific type of product (e.g. influenza virus type A or rotavirus type C) and for a specific host (e.g. swine) or hosts, a production platform proposed for biologics use can itself be evaluated, with a possible subsequent reduction in individual product testing of that agent- specific type and for that host(s). This Summary Information Format is for use in such an evaluation.

A. Objective

1. Identify where the Production Platform for Regulated Biological Agents was constructed and where the products will be made, tested and manufactured. Address the available level of containment.

2. Provide a brief description of the Production Platform for the Regulated Biological Agents.

3. Identify the proposed Regulated Biological Agents to be manufactured using the Production Platform.

4. Indicate why a Production Platform approach is appropriate for the proposed group of Regulated Biological Agents.

B. Proposal

1. What is the proposed use of the products derived from the Production Platform? If more than one type of agent-specific product for a specific host(s) is proposed for manufacture and licensure using the Production Platform, the firm must submit a SIF-IV to the CVB for the first Production Platform construct for each type. For example, if products for influenza virus type A in swine will include a vaccine containing two hemagglutinin (HA) genes (H1 and H3), a vaccine containing four HAs (2 H1s and 2 H3s), and a vaccine containing an HA and a neuraminidase (NA) gene, the first construct per license for each of the three vaccines should be described in separate SIF-IV documents, as should a product for a new target species not previously evaluated in a SIF-IV.

a. Species
b. Proposed claim
c. Geographic area
d. Route of administration
e. Brief description of the expected safety profile

II. Description of the Production Platform for Regulated Biological Agent Construction

A. The Backbone Biological Agent and Host, if any

1. What organism was used for the Backbone Biological Agent? Does it require a host cell? If so, what is the host cell and its relationship with the Backbone Biological Agent? Are there any known virulence features associated with the Backbone Biological Agent or the host cell? Will any part of the Backbone Biological Agent be present in the final product? What happens in the target species? [Add scientific citations, if appropriate.]

    a. What is the previous safe use of the Backbone Biological Agent and host cell?

        (1) If available, provide the history of previous safe use, using published literature or internal documents. Include the recommended CDC/NIH biosafety level for use of the Backbone Biological Agent and host cell. [This may be the first document on safe use of the Backbone Biological Agent.]

2. Physical characteristics of the Backbone Agent

    a. Provide a flow diagram or explanation of the process of how the Backbone Biological Agent was constructed.

        (1) Describe the proposed site(s) for Donor DNA or RNA insertion.

        (2) Do the flanking regions of the proposed insertion site in the Backbone Biological Agent have any known regulatory elements that could moderate the expression of the inserted Donor DNA or RNA?

        (3) If possible, identify unique restriction endonucleases (not more than five) that will give identifiable digestion patterns useful for characterizing the final Backbone DNA or RNA.

        (4) Provide primer sequences that will allow sequencing of the Backbone Biological Agent, at least the sequences flanking the genetic insert(s).

B. Donor Biological Agents and Donor DNA, RNA or Genes

1. What are the Donor Biological Agents used as the source of each Donor Sequence inserted into the Backbone Biological Agent?

a. Has there been safe use of the Donor Biological Agents, Donor Gene(s), and /or Donor Sequence(s)?

(1) Provide relevant references for safe use.

b. Are there specific parts of the Donor Gene(s) or Sequences that were used for insertion?
c. Provide entire or pertinent sequences or restriction endonuclease sites of the Donor Biological Agents, Donor Gene(s) or Donor Sequence(s).
d. Describe the product of the Donor DNA, RNA, or Gene(s) and how it is characterized.

C. Construction and Characterization of the Regulated Biological Agents

1. Provide a flow diagram on the construction of the Regulated Biological Agents. Include the following:

a. Final Backbone Biological Agents
b. Donor DNA, RNA or gene and relevant restriction sites
c. All shuttle vectors
d. Host cell lines or cells used
e. Selection techniques and methods used to construct the final Regulated Biological Agents

2. Describe the laboratory methods or criteria used to evaluate the Regulated Biological Agents.

3. Physical characterization of the Regulated Biological Agents

a. Characterize the physical map of the Regulated Biological Agents, using unique Donor DNA or RNA and Backbone Biological Agent restriction endonuclease sites, and describe resulting restriction fragments and digestion patterns.
b. Devise a PCR or restriction endonuclease test based on the Backbone Biological Agent sequence and the Donor Sequence that will identify and characterize the Donor DNA or RNA/Backbone Biological Agent construct.
c. Cite methods used to purify the final product.
d. What will be the criteria for stability of the initial Regulated Biological Agent Master Seed (n) and the highest passage of the Master Seed to be used for production (n + x)?

(1) What laboratory procedure will be used to demonstrate that the Regulated Biological Agent is producing the desired product?

(2) What laboratory procedure will be used to demonstrate that the sequence of the MS (n) is identical to the sequence of the MS (n+x)?

e. Provide genetic sequences in electronic format for the initial inserted gene(s) or altered sequence(s) of the Regulated Biological Agent, including flanking sequences where appropriate. Also provide in electronic format any new or variant genetic sequences for additional Regulated Biological Agents manufactured using the Production Platform.

4. What is the recommended CDC/NIH biosafety level for the Regulated Biological Agents?

5. Provide a short summary or description of genetic motifs that may have resulted as a consequence of the genetic recombination (II.C.3.d). Are there any known motifs that may promote homologous recombination, DNA insertion, or gene expression of existing or new open reading frames?

III. Glossary

A. 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 Biological Agent, including replication and regulatory sequences.

B. 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.

C. 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.

D. 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.

E. 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).

F. 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.

G. *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.