TO: Biologics Licensees, Permittees, and Applicants  
Directors, Center for Veterinary Biologics  
Veterinary Services Leadership Team

FROM: Byron Rippke  
Director

SUBJECT: Update for Documenting Appropriate Details for Potency Tests

I. PURPOSE

The purpose of this Notice is to update industry regarding expectations for the level of detail required in Section V.C. of Outlines of Productions (OPs) and associated Special Outlines (SOs). Although the majority of information described below is specific to vaccines or immunotherapies administered to animals, the general concepts are applicable to all products under CVB’s jurisdiction. This Notice is not intended to require modifications to assays described in OPs or SOs but rather clarify the current assay procedures being used.

CVB Notice 20-11 was published in 2020 with the same intent as the current document. After discussions internally and with industry, it has been determined that additional details are required to clarify CVB’s expectations. The CVB intends to update Veterinary Services Memorandum (VSM) 800.206 to address these clarifications more appropriately. The following Notice states the CVB’s expectation of OPs and SOs outside of the forthcoming memo and specifies some of what will be further clarified in VSM 800.206.

The current notice replaces Notice 20-11 which has been removed from the Center for Veterinary Biologics’ (CVB) Website.

II. BACKGROUND

Title 9, Code of Federal Regulations, part 113.5 (a) requires satisfactory completion of potency testing of all serials of biological products before they are released for marketing. Part 114.9 (c) – (f) lists the OP requirements for different types of products and all state that tests must be described in detail within Section V. Testing. Veterinary Services Memorandum No. 800.206 states that OPs or related SOs should “Include stepwise procedures in sufficient detail so a laboratory technician experienced in general laboratory techniques could perform the assay.” Descriptions will vary based on what is being tested, but the expected level of detail includes the specific reagents required, the number of vials or samples tested, the testing performed on each, objective decision-making step(s) for selecting subsets of wells/dilutions/plates/etc. used in later steps, validity criteria and calculations required to determine potency in a way that the reader
could reproduce the results from the licensee or permittee. Analogous information for diagnostics would include the number of plates/devices/wells that are used, any calculations that are required to determine the classification, and any cutoffs or controls that are required for serial release that may not be in the insert or used by the end user.

III. ACTION

During the annual reviews, as required by 9CFR 114.8(d), OPs and SOs should be reviewed for clarity and updated to consider including additional details at the level an independent laboratory could reproduce the test in the same manner it is conducted by the firm. The following list reflects some examples of common situations where clarity is lacking. For some, specifics regarding the level of detail expected will be forthcoming in an update of VSM 800.206 and those are noted along with possible solutions that have been discussed. A consideration should be made that CVB should be able to independently verify the results and validity of a test with documents that are on hand rather than requesting current use information for a given test. These have been written to apply to all assay types, so not all information will be applicable to a given assay, but analogous information should be provided for all potency tests at a similar level of detail:

1. The number of vials, or the number of samples if taken from bulk, used for conducting the potency test for the test serials, controls, reference and any other preparation used in the assay. If more than one vial has been used historically, indicate that to avoid confusion between historic practices and new policy.

2. Specify all level of detail for a given vial for each preparation. Examples include dilution factors, number of dilution series created, number of plates per dilution, countable range, etc. Include decision processes for selecting dilutions within the series or plates within a set, where applicable. Specify all calculation methods for each vial.

3. If a single potency measurement is derived from multiple vials, update the OP or SO to indicate the method for combining results across vials (i.e., arithmetic or geometric mean) and specify that value is used for serial release using the existing potency specifications. Do not alter current release or expiration potency specifications.

4. If a test control is used to determine the validity of an assay run, identify the control and include validity requirements in the Outline. This will be further discussed in VSM 800.206, but CVB will likely entertain the following options:
   o Provide the lot number of the control preparations in the applicable OP. This is not the same specifying formulation information alone which is not sufficient.
   o Lot control preparations used across multiple products in a single SO that is referenced by all applicable OPs.
Establish validity criteria (ranges) during assay validation and continue their use regardless of the lot of control product in use. When a control requires replacement, one will be formulated to target the existing range in the OP.

5. Clearly and objectively state any other validity criteria or inclusion criteria, such as methods for selecting a single dilution or determining countable ranges, in the OP.

6. A sample calculation would be helpful for inclusion in the filed documentation.

7. Critical reagents will be further defined in the VSM 800.206 update to indicate reagents that effect or change the architecture of the test which will require re-validation. It is noted that “critical reagents” will vary across assay methods which will also be discussed more in the memo. Lot changes for critical reagents will still only require demonstration of equivalence as described in VSM 800.112 Appendix III Section 2.4.6.2 for relative potency ELISAs.

IV. IMPLEMENTATION/ APPLICABILITY

Implementation will be addressed with the revision of VSM 800.206 but will be at least 2 years beyond that noted in Notice 20-11; no earlier than April 2024.