USDA
United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

Center for Veterinary Biologics

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CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 23-08

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

FROM: Dr. David White
Acting Director

DAVID WHITE Digitally signed by DAVID WHITE
Date: 2023.04.09 14:20:10 -05'00'

SUBJECT: Update for Documenting Appropriate Details for Potency Tests

I. PURPOSE

The purpose of this Notice is to remind industry of the expectations for the level of detail required in Section V.C. of Outlines of Productions (OPs) and associated Special Outlines (SOs). Although most of the 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 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 considered for release to the marketplace. 9 CFR 113.6 authorizes CVB to examine and test serials for purity, potency, safety, or efficacy as a part of the market release process. Part 114.9 (c) – (f) lists the OP requirements for different types of products and each of these sections say that tests must be described in detail within the appropriate testing section of the OP. Veterinary Services Memorandum No. 800.206, Appendix I, Section V. states that OPs 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 the test, 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.

CVB should be able to independently verify the results and validity of a test with documents that are on hand rather than having to request current use information for a given test. When test procedures are not fully described in documents that are on file at CVB, review and testing time may be increased due to the need to request missing information.

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 could be improved. 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.

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/wells 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, the OP or SO should indicate the method for combining results across vials (i.e., arithmetic or geometric mean) and clearly specify the derived value is used for serial release. Do not alter current release or expiration potency specifications.

4. Consider including a sample calculation in the file documentation to help the reader fully understand the described procedure.

5. Clearly and objectively state any validity criteria or inclusion criteria, such as methods for selecting a single dilution or determining countable ranges, in the OP. Additional expectations for test controls and validity criteria will be addressed in a VSM 800.206 update.

6. Critical reagents will be further defined in the VSM 800.206 update. CVB considers those to be any reagents that effect or change the architecture of the test. Changing a critical reagent will require validation according to VSM 800.112. It is noted that critical reagents will vary across assay methods which will also be discussed further 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

CVB will comment on missing information in Outlines and Special Outlines. Items specific to the VSM 800.206 update will have implementation addressed when that memo is updated.