Veterinary Services Memorandum 800.116

Laboratory and Target Animal Batch Safety Testing Exemption

1. Purpose and Background

This memorandum provides guidance to licensed and permitted firms on requesting an exemption under title 9, *Code of Federal Regulations* (9 CFR), part 113.4, to laboratory animal batch safety testing (LABST), as required in Section V.B. of the Outline of Production (OP) and 9 CFR 113.64, 113.100, 113.113, 113.200, 113.300, and 113.450, or to target animal batch safety testing (TABST), as required in Section V.B. of the OP and 9 CFR 113.64, 113.100, and 113.300. The Center for Veterinary Biologics (CVB) will consider granting an exemption to LABST and TABST for specific products with a documented history of acceptable safety results and controlled manufacturing processes that have ensured batch-to-batch consistency and sterility.

Safety testing in animals has been a component of the approval process for each serial of product CVB has released for marketing since the program's inception. This safety release testing provides assurance that each serial of product will not have unfavorable results in the target animal. General safety requirements for live bacterial vaccines are described in 9 CFR 113.64, inactivated bacterial products in 9 CFR 113.100, autogenous biologics in 9 CFR 113.113, killed virus vaccines in 9 CFR 113.200, live virus vaccines in 9 CFR 113.300, and antibody products in 9 CFR 113.450.

Depending on the type of product, LABST may be conducted in the mouse (9 CFR 113.33) or the guinea pig (9 CFR 113.38) and TABST may be conducted in the cat (9 CFR 113.39), dog (9 CFR 113.40), calf (9 CFR 113.41), pig (9 CFR 113.44), sheep (9 CFR 113.45), poultry (9 CFR 113.100(b)(2)), or aquatic species or reptiles (9 CFR 113.100(b)(3)). If the Standard Requirement (stipulated in 9 CFR) for a product does not specify the animal safety test method, Section V.B. in the Outline of Production (OP) must indicate a method and state the animal species to be used in safety testing. With the number of serials produced by all licensed manufacturers, the number of animals used for safety testing can be substantial.

Some products may have established historical data documenting product safety and consistency in manufacturing processes, mitigating the need for continued LABST or TABST. CVB's consideration of an exemption to LABST or TABST is consistent with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) Steering Committee's recommendations described in "*Harmonisation of Criteria to Waive Laboratory Animal Batch Safety Testing for Vaccines for Veterinary Use*" (LABST; GL59), "*Harmonisation of Criteria to Waive Target Animal Batch Safety Testing (TABST) for Inactivated Vaccines* (TABST; GL50) and "*Harmonisation of Criteria to Waive Target Animal Batch Safety Testing for Live Vaccines for Veterinary Use*" (TABST; GL55),

intended to minimize the use of LABST and TABST and following the principles of reducing, refining, and replacing the use of animals in testing.

2. Document Status

   A. Issue Date: 05/16/2025.

   B. This document replaces Veterinary Services Memorandum (VSM) 800.116 dated August 14, 2017, which is cancelled.

3. Reason for Reissuance

   The VICH guidelines have been finalized for *Harmonisation of Criteria to Waive Laboratory Animal Batch Safety Testing for Vaccines For Veterinary Use*. CVB, as a member of the VICH group that developed the guidelines, is now able to revise this document. The revision changes the memo title, as the memo will apply to target-animal and laboratory-animal batch safety testing. The revision provides additional clarity to licensees/permittees seeking an exemption.

4. Authority and References

   A. Authorities

   - Virus-Serum-Toxin Act
   - 7 CFR 371.4
   - 9 CFR 102.5
   - 9 CFR 113.4
   - 9 CFR 113.33
   - 9 CFR 113.38
   - 9 CFR 113.39
   - 9 CFR 113.40
   - 9 CFR 113.41
   - 9 CFR 113.44
   - 9 CFR 113.45
   - 9 CFR 113.64
   - 9 CFR 113.100
   - 9 CFR 113.113
   - 9 CFR 113.200
   - 9 CFR 113.300
   - 9 CFR 113.450
   - 9 CFR 116.5
   - 9 CFR 116.9

B. References

- "*Harmonisation of Criteria to Waive Laboratory Animal Batch Safety Testing for Vaccines for Veterinary Use*" (LABST; GL59)
- "*Harmonisation of Criteria to Waive Target Animal Batch Safety Testing (TABST) for Inactivated Vaccines*" (TABST; GL50)
- "*Harmonisation of Criteria to Waive Target Animal Batch Safety Testing for Live Vaccines for Veterinary Use*" (TABST; GL55)
- VSM 800.53, Serial Release of Licensed Biological Products
- VSM 800.57, Market Suspensions and Post Marketing Temperature Deviations
- VSM 800.100, Exemption from Using Heat or Ionizing Radiation to Treat Equine Plasma Used in Manufacturing Plasma Products for Oral or Parenteral Administration to Horses Under 9 CFR 113.450(e)(1) and Exemption from the Mouse Safety Test Under 9 CFR 113.450 (i)
- VSM 800.117, Guidance for Inactivation Studies
- VSM 800.125, Preparation and Submission of Adverse Event Reports for Biological Products by Licensees and Permittees
- VSM 800.210, Manufacturing Deviations Identified Prior to Marketing Release

5. Audience

VS employees and members of the biologics industry.

6. Guidance

A. CVB will consider exemption requests to LABST and TABST for a fully licensed or permitted product with documented consistency in manufacturing processes and a well-documented and continuously evaluated history of product safety and sterility. A TABST associated with the final product potency assay, such as vaccination-challenge potency assays in poultry or aquaculture, will not be considered for an exemption. CVB will not currently consider exemptions for products with an inherent safety risk, such as known significant adverse events, or agents of public health significance, such as rabies virus.

1) Prior to requesting an exemption for inactivated products, and if not already completed, satisfactorily complete an inactivation kinetics study according to VS Memorandum 800.117 for each inactivated fraction and submit the report that includes information on the confirmation of the inactivation test method assay. A study may not be needed for a product with an inactivation kinetics study approved prior to August 12, 2013, if the inactivation is performed according to the parameters approved in that study, and additional approved modifications as stated in the OP with the approval date(s); the data should be on file with CVB for review.

2) Prior to requesting an exemption, ensure the OP of the product contains adequate

production details of the manufacturing process and that all serials submitted as part of the exemption request were manufactured according to the most current version (i.e., modifications or changes to the OP or Special Outline (SO) were made prior to the production of the serials submitted as part of the exemption request). This may also apply to the associated SO.

3) The report submitted with an exemption request must provide an overall assessment of all aspects of the product's safety performance and confirm consistent manufacturing processes.

   CVB expects submission of a dataset that demonstrates manufacturing consistency. If these criteria cannot be met in specific manufacturing situations, firms may submit a proposal to CVB justifying a different scope of data to be collected to show safety performance and manufacturing consistency.

   Exemption requests for fallout products of larger combinations require a separate exemption submission but can be supported by these same data.

4) The report must include the following to document consistency in manufacturing and an acceptable safety profile:

   a. *Serial summary*. The data must describe ten (10) recent serials manufactured according to the OP and associated SO(s) from at least 1 (one), but not more than 5 (five), years before the date of request. The serials for consideration must have been produced after full licensure and can be non-consecutive but must be from at least three (3) different consecutive antigen bulks for each antigen used in formulation of the final product (i.e., sub-serials will not be included in the total number of serials considered for demonstrating consistency). Indicate in the report these are the serials submitted to support the request for the exemption.

      Include all serials produced during the time-period covered by the report, even if they do not contribute data to the exemption evaluation. Firms must disclose information regarding any serial(s) produced between the non-consecutive serials submitted for consideration that failed serial release testing.

   b. *Laboratory animal batch safety test method* (for LABST). Briefly describe the current procedure for conducting the laboratory animal safety serial release test, including the validity criteria and parameters of acceptable test outcomes. Include references to the current version of the OP and any associated SOs used in testing.

   c. *Target animal batch safety test method* (for TABST). Briefly describe the current procedure for conducting the target animal safety serial release test, including the validity criteria and parameters of acceptable test outcomes.

Include references to the current version of the OP and any associated SOs used in testing.

d. *Animal batch safety test results.* Submit results for LABST and/or TABST testing conducted for the serials submitted, including test results designated as No Test or Inconclusive or Unsatisfactory. The bench records, with daily observation results, for the safety testing during the time-period must be available upon request.

   For a TABST exemption, include the range of ages for the animals used to conduct serial release safety testing. If different aged animals were used, provide a percentage of the total for each age used. Also include the investigation outcome for test results that were coded as No Test or Inconclusive or Unsatisfactory. Describe and justify differences between the age ranges used in testing and those expected for use in the field.

e. *Sterility test results.* Submit sterility test results for bacteria, fungi, and mycoplasma for the serials submitted, including test results designated as No Test or Inconclusive or Unsatisfactory. To ensure manufacturing consistency, firms are encouraged to define a satisfactory test result as no growth in any vessel as opposed to the retest procedures outlined in 9 CFR 113.

f. *Maximum antigenic content specification.* Submit how antigenic input per dose is calculated for each fraction, and the values for each fraction, for the serials submitted in support of the exemption request.

   The request for the exemption must propose a specification for the maximum antigenic content allowed in serials. The specification can use a broader range of data than submitted for the exemption request. The specification can be no larger than the maximum (i.e., 1X) observed value from any acceptable serial within the acceptable time frame with a proven safety profile. Data used must cover a minimum of one (1) year (or ten (10) consecutive serials) but no more than five (5) years (or one hundred (100) consecutive serials). Historical data for the past three (3) years in most cases should be adequate.

   1. Reevaluate the maximum antigen content specification if adverse events are detected in the firm's Pharmacovigilance (i.e., Product Monitoring) program.

   2. The firm may submit supportive data for an alternative specification for consideration, such as data from recent 2X or 10X safety testing, overdose studies, repeat-dose studies, and/or field safety studies, but these data cannot be substituted for the data required above.

g. *Pharmacovigilance data.* Submit a Product Safety Assessment covering the history of the product to the present. Include an analysis and assessment of all known adverse events associated with the product, including frequency, severity, duration, determination of causality, and any investigations into the likely causes of these events. Confirm the raw data for these serials is submitted to CVB in accordance with 9 CFR 116.9 and VSM 800.125.

h. *OP and SO(s) revisions.* If minor revisions have been made during the timeframe for the serials submitted in support of the exemption, submit a synopsis of changes, focusing on manufacturing and/or serial release testing changes, and justify the effect of the revision on the safety of the product.

i. *Product history.* Submit a summary of technology transfers (between and within licensees/permittees) from the time of product licensure. State the history of Product Code Number changes and the history of acquisitions, buyouts, or mergers for the product if applicable. Include the number of batches manufactured, the number of years the product has been on the market, and the number of doses sold.

5) Plasma products administered by the oral or parenteral route are exempt from 9 CFR 113.450(i) for LABST if the procedures listed in VSM 800.100 are met.

6) When granted, the LABST and/or TABST exemption will be effective when the OP and/or SO is updated and approved. Required updates are listed below, but the firm should include any other conditions of the exemption that may apply to risks specific to the product being considered. The laboratory or target animal batch safety test procedure in Section V.B. of the OP/SO must be maintained if safety testing is required, or in the event the exemption is suspended or revoked.

   a. Include the date of the approval and Mail Log number of the TABST and/or LABST exemption in Section V.B. of the applicable OP/SO.

   b. State the maximum antigen content per dose for each fraction in Section IV.I. of the OP/SO and provide a minimum and maximum antigen content per dose(s) in the final container.

7) The pivotal field safety study described in the Individual Study Summary (ISS) must fully document the study even if the report was submitted to CVB for approval prior to January 1, 2007. This applies to all field safety studies conducted for licensure of each product for which a TABST and/or LABST exemption is granted. If a placeholder ISS has been previously approved for use in the published product summary, the licensee/permittee must separately submit a revised, full ISS at the time of submission of the OP. Once the revised ISS is approved, CVB will post the revised product summary on the APHIS website.

B. Notification of Issues

Firms must notify CVB of issues that could affect the quality of a serial or product. If a serial is not produced in conformance to the OP, associated SO(s), or applicable regulations, the establishment may use the regulatory flexibilities as outlined in VSM 800.210 prior to market release. Submission of the APHIS Form 2008 must include a remark briefly describing the non-conformance and indicating that the firm investigated the manufacturing deviation, as well as the result supporting that the product will perform as intended throughout the shelf-life of the product.

1) In some cases, it may be appropriate to conduct the animal safety test and report the outcome as part of the investigation.

2) If at any time there are indications that the quality of the product is or may be affected, either through internal quality processes or through signal detection in the firm's pharmacovigilance system, contact CVB Inspection and Compliance as per 9 CFR 116.5(b). During an inspection, if CVB determines a product is not prepared in accordance with the OP, SO(s), or regulations, it will consider this a serious violation of 9 CFR 102.5(c)(1) and will take appropriate regulatory actions.

3) In the event of a major manufacturing change and/or technology transfer, follow the general procedures outlined in VSM 800.53 Section B.5.c. and VSM 800.87 Section IV.L.. The firm must submit the changes to their Reviewer along with a proposal to show equivalence between the serials produced before and after the change. The proposal may include additional *in vitro* or live animal testing, increased reporting requirements, or other factors that assure continued manufacturing consistency and safety.

4) Suspension: CVB retains the right to assess the totality of the facts when assessing manufacturing deviations and/or product quality issues. It gives significant weight to the magnitude of the production nonconformities and/or willful issues regarding their ongoing effect on final product manufacturing, testing, safety, or purity.

   a. If suspended, the firm must perform the LABST or TABST as stated in Section V. of the OP/SO, and results reported on the APHIS Form 2008.

   b. A suspension may progress to revocation if the firm does not show adequate progress toward correcting the issues CVB identifies within three (3) years of a suspension.

5) Revocation: CVB may revoke an exemption if it finds egregious and/or willful issues in manufacturing or reporting, and/or has concerns regarding ongoing product testing, safety, or purity issues. Once revoked, the LABST or TABST must be performed as stated in Section V. of the OP and results reported on the APHIS Form 2008.

6) Reissuance: CVB may reissue a suspended or revoked exemption if the firm submits adequate information that demonstrates the production process is controlled, and the product is safe and pure. Submit the required information as stated in Section 6.A. of this memo for serials manufactured after resolution of issues identified by CVB.

7. Implementation/Applicability

Updated policy in this memorandum is effective immediately.