



ANIMAL USE REDUCTION US INDUSTRY PERSPECTIVE

US ANIMAL HEALTH INSTITUTE - ANIMAL USE REDUCTION WORKING GROUP

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USDA/APHIS/VIS/CVB SAFETY TESTING

- Classic approach for Animal Batch Safety Testing in US
 - Unfavorable reactions attributable to the biological product occur during the observation period, the serial is unsatisfactory.
- Safety Testing Regulated by 9 Code of Federal Regulations (CFR) Part 113

TARGET ANIMAL BATCH SAFETY TESTING

- TABST regulated by
 - 9CFR113.39 cat
 - 9CFR113.40 dog
 - 9CFR113.41 calf
 - 9CFR113.44 swine
 - 9CFR113.45 sheep
 - 9CFR113.100 (b) (2) poultry
 - 9CFR113.100 (b) (3) aquatic species
 - 9CFR113.200 horse



LABORATORY ANIMAL BATCH SAFETY TEST

- LABST regulated by
 - 9CFR113.33 mouse
 - 9CFR113.38 guinea pig



PUBLICATION OF USDA TABST EXEMPTION

- USDA/APHIS/VS/CVB Veterinary Services Memorandum (VSM) No. 800.116 - *Target Animal Safety Testing Exemption* – published August 2017
- USDA's consideration of an exemption to target animal batch safety testing is based on the VICH Steering Committee's recommendations described in GL50 (Inactivated Vaccines May 2017) and GL55 (Live Vaccines May 2017) aimed to minimize the use of **target animal batch safety tests** and the principles of reducing, refining, and replacing the use of animals in testing (3Rs).

VSM 800.116 REQUIREMENTS

- The CVB will consider exemption requests for all products with documented consistency in manufacturing processes and product safety with the exception of safety tests associated as precursors to potency tests.
- Few firms have obtained the product TABST exemption to date.
- Global evaluation of safety testing and PV data have shown this safety testing does not correlate well to safety in the field. (Reference VICH Guideline GL59)
 - Only a few veterinary vaccines show inherent batch-dependent safety risk, which might be due to residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines.

VSM 800.116 REQUIREMENTS

- A submitted report should provide an overall assessment of all aspects of the product's safety performance, including serial release and pharmacovigilance data (number of years on the market, number of doses sold, frequency and severity of adverse event reports). Specific data for 10 serials, or a minimum of 5 serials if 10 serials are not manufactured within 3 years, should be submitted. The serials should be consecutive and from different vaccine bulks. Fallout products of larger combinations may be supported by these data. Information on any serials failing animal safety testing or deviating from the Outline of Production during this time period should be disclosed.

VSM 800.116 REQUIREMENTS

- To ensure that products exempt from safety testing in animals perform in the field as expected, the licensee or permittee must maintain detailed pharmacovigilance records for all adverse event reports received for the respective products they produce or distribute. For products receiving this exemption, summaries of adverse events should be provided to the CVB annually per license restriction.
- Updated regulations 9 CFR, 116.9, requires veterinary biologics licensees to submit all adverse event reports to the CVB.

CVB PHARMACOVIGILANCE RECORDS

- August 2020 - Issuance of VS Memorandum 800.125 - *Preparation and Submission of Adverse Event Reports for Biological Products by Licensees and Permittees*
 - Developed XML File Format and Web Based Ex Transmissions to Agency
 - Gateway
 - PV Express II
 - Data follows VICH Guidelines GL24 and GL42
 - Immediate and Periodic Reporting Schedules and Follow-up AERs
- CVB may require the below be pre-requisites to move toward exemption of safety test(s)
 - CVB ability to determine signals and trends at the serial level vs product level
 - Increase accuracy of serial numbers in AER
 - Correlate/map international codes with USDA Product Codes

VSM 800.116 REQUIREMENTS

- Outlines of Production may require updates including additional product specifications for maximum antigen content based on safety test information, historical antigen input, etc. Changes to the Outline of Production open up the exemption for reexamination.

2017 AHI REQUEST TO USDA FOR ELIMINATION OF COMPENDIAL ANIMAL SAFETY TESTING

Elimination of Compendial Animal Safety Testing: #USDA-2017-0002-4101

PROPOSAL: AHI proposes that APHIS amend its regulations in title 9 of the Code Federal Regulations to eliminate requirements for batch safety testing conducted in animals.

To Date: No action from USDA on the proposal. *COVID possibly a contributing factor.*

REVISION TO VSM 800.116 TO ADD LABST

- Draft VSM Document 650 – *Laboratory and Target Animal Batch Safety Testing Exemptions* - published for comment August 2020.
- USDA's consideration of an exemption to laboratory animal batch safety testing is based on the VICH Steering Committee's recommendations described in GL59 (November 2020) aimed to minimize the use of **laboratory animal batch safety tests** and the principles of reducing, refining, and replacing the use of animals in testing (3Rs).

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

- CVB will consider exemption requests for products with documented consistency in manufacturing processes and product safety and sterility, with the exception of safety tests associated as precursors to final product testing or potency assays. However, for products with an inherent safety risk such as significant adverse events, or agents of public health significance such as rabies virus, animal safety testing generally will need to be conducted for each serial to confirm the product does not cause unfavorable results in the target animal and to ensure batching consistency.
- Prior to requesting an exemption for inactivated products, satisfactorily complete an inactivation kinetics study according to VS Memorandum 800.117 for each fraction inactivated and validate the assay that is used to assess complete inactivation (new requirement for licensed products already being supplied to the market).
- Prior to requesting an exemption, **Outlines of Production** may require updates including additional product specifications for maximum antigen content based on safety test information, historical antigen input, etc. Changes to the Outline of Production open up the exemption for reexamination.
- Summarize all manufacturing modifications or changes made prior to the production of the serials that were submitted as part of the exemption request. This may also be applicable to the associated Special Outlines (SOs). The confirmation of dating must be approved and stated in the OP. Changes to the OP and SOs may open up the exemption for reexamination.

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

- A submitted report with an exemption request should provide an overall assessment of all aspects of the product's safety performance, including serial release and pharmacovigilance data (number of years on the market, number of doses sold, frequency and severity of adverse event reports). Specific data for the last 10 serials, or a minimum of 5 serials if 10 serials are not manufactured within three (3) years, should be submitted. The serials should be consecutively manufactured according to the OP and associated SOs. Each serial must be formulated from different antigen bulk. Fallout products of larger combinations may be supported by these data. Information on any serial(s) failing serial release testing during this time period should be disclosed. Deviations in manufacturing or testing from the OP and associated SOs during this time period should also be disclosed.

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

- The report must include the following to document consistency in manufacturing and an acceptable safety profile:
 - *Laboratory animal batch safety test* (for LABST exemption only). Describe the procedure for conducting the laboratory animal safety serial release test, including the validity criteria and parameters of acceptable test outcomes.
 - *Target animal batch safety test* (for both LABST and TABST exemptions). Describe the procedure for conducting the target animal safety serial release test, including the validity criteria and parameters of acceptable test outcomes.
 - *Data submission*. Submit results for laboratory and/or target animal batch safety testing conducted. Provide justification for retests. The bench records, with daily observation results for each animal, for the safety testing during the time period should be included.

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

- *Specific sterility data for serials.* Sterility test results for bacteria, fungi, and mycoplasma during the time period should be included.
- Maximum antigenic content. Antigenic input per dose for each fraction for the ten serials should be included. The request for exemption should also include the proposed maximum antigenic content.
- *Pharmacovigilance data for serials within the past ten (10) years or since licensure, whichever is shorter.* Provide a summary of data covering adverse events for product sold and distributed. Any known adverse events associated with the product should be disclosed, including frequency, severity, duration, and determination of causality. Disclose the number of doses sold and distributed.
- OP and SO(s) revisions. Provide a synopsis of manufacturing and serial release testing changes since licensure including changes resulting from acquisitions, buyouts, or mergers if applicable.
- Product history. Include 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.

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

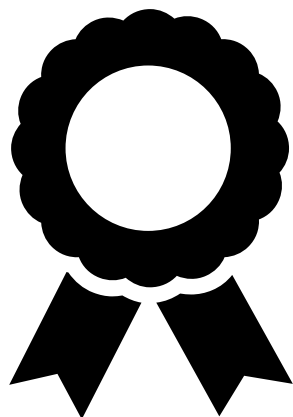
- When an exemption is granted, the laboratory or target animal safety test procedure in Section V.B. of the OP must be maintained for testing in the event the exemption is suspended or revoked.
- When an exemption is granted, the maximum antigen content, based on safety information and historical antigen input for each fraction, will also be approved. The LABST or TABST exemption will be effective once the OP is updated to reflect maximum antigen content and the date of exemption. The maximum antigen content is calculated as the geometric mean result from a minimum of five of the ten serials with the highest antigen input and without adverse events correlated to antigen input. Alternatively, the maximum antigen content may be determined as the antigen input from the prelicense serial administered during the field safety trial to one-third of minimum age target animals per the label claim with minimal or no adverse events correlated to antigen input.
- The pivotal field safety study Individual Study Summary 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 exemption is granted.
- To ensure that products exempt from safety testing in target animals perform in the field as expected, the licensee or permittee must maintain detailed pharmacovigilance records for all adverse event reports received for the respective products they produce or distribute. For products receiving this exemption, summaries of adverse events should be provided to CVB annually per license restriction.

VSM DRAFT 650 REGULATORY OBSTACLES FOR INDUSTRY

- If a serial is manufactured with nonconformance to the OP or in the event of unfavorable pharmacovigilance report updates, an exemption may be suspended. Reissuance of the exemption will require adequate information demonstrating that the production process is controlled, including the provision of satisfactory safety test results for 10 consecutive serials, or 5 if made infrequently.
- If manufacturing changes are made to the OP or associated SO(s), the exemption may be suspended. Depending on the significance of the change, additional data and/or serial safety testing may be required to continue the exemption.
- An exemption may be suspended if production nonconformities discovered during onsite inspection could have a material effect on the expected product profile, as determined by CVB-Inspection and Compliance staff.

IN PLACE ACROSS US FIRMS

- **Quality systems:** Good Manufacturing Practices (GMP) and similar quality systems have been established to cover the manufacture and testing of biological products. These quality systems provide assurance that veterinary vaccines placed on the market have been manufactured in a consistent and suitable manner.
- **Seed lot system:** The establishment of a seed lot system, subject to quality and manufacturing controls, provides further assurance of the consistent production of vaccine batches and resulting batch quality.
- **Pharmacovigilance:** Post-marketing surveillance of vaccines. This provides for early detection of safety problems associated with the inconsistent quality of a vaccine in the field. Pharmacovigilance provides extra information about the product's safety that cannot always be obtained in the LABST requirements only. Available PV data should be provided using recent Product Safety Update Reports (PSUR) for the relevant time period.



SUCCESS - PENDING PUBLISHED GUIDANCE

- VSM 800.67- Shipment of Experimental Veterinary Biological Products guidance to industry proposes revisions to remove animal safety testing as a requirement for requesting 9 CFR 103.3 authorization to ship experimental vaccines for *in vivo* use.
- Updates are pending USDA finalization and publication.