

4.5.1 Target Animal Safety Testing Exemption

1. Overview

Safety testing in animals has been a component of the approval process for each serial of product released by the Center for Veterinary Biologics (CVB) since the Program's inception. This serial release testing is conducted to provide assurance that each serial of product will be safe in the target animal and without adverse reactions, local or systemic. Depending on the type of product, animal safety testing may be conducted in mice, guinea pigs, or the host or target animal. The Standard Requirement (SR) must be specified in the Outline of Production. If the SR (stipulated in Title 9, Code of Federal Regulations) for a product does not specify the animal safety test method, Section V.B of the Outline of Production must specify a method and state the animal species to be used in safety testing.

With the number of serials produced by all currently licensed and permitted manufacturers, the number of animals used for safety testing is substantial. Historical data for some products indicate no adverse safety or sterility testing results have occurred. Historical data would include data collected post licensure. The timeframe would depend on the type of product and number of serials produced and tested. Data generated from all products with similar platform based systems may be considered to support the exemption for a single platform technology product, with appropriate justification, including consideration of consistency in formulation, equipment, and location, timing (e.g., campaigning), and method of production. In addition, many products in the biologics industry are manufactured under well-documented manufacturing processes and under Outlines of Production with parameters set to control process variation. These products have a history of safety and consistency in manufacturing processes and may be considered as candidates for an animal safety testing exemption.

The procedure to consider an exemption from target animal safety testing is presented below. It applies to all products for which target animal safety testing is currently specified in Section V.B. of the Outline, and to all target animal safety testing specified in Section V.B. of those Outlines. The USDA's consideration of an exemption to target animal safety testing is consistent with the VICH Steering Committee's recommendations aimed to minimize the use of target animal safety tests and the principles of reducing, refining, and replacing the use of animals in testing.

2. Related Documents/Regulations

- Veterinary Services (VS) Memorandum No. [800.116](#) Animal Safety Testing Exemption
- VSM [800.204](#) (for guidance regarding adverse event reporting)
- VSM [800.100](#) (exemption to mouse safety testing for equine plasma products)
- 9 CFR [113.100](#) General safety requirements for inactivated bacterial products
- 9 CFR [113.200](#) General safety requirements for killed virus vaccines
- 9 CFR [113.300](#) General safety requirements for live virus vaccines
- 9 CFR [113.40](#) Dog safety testing
- 9 CFR [113.39](#) Cat safety testing

- 9 CFR [113.41](#) Calf safety testing
- 9 CFR [113.45](#) Sheep safety testing
- 9 CFR [113.44](#) Pig safety testing
- 9 CFR [113.100\(b\)\(3\)](#) Poultry, and aquatic species safety testing

3. Procedures

An exemption to target animal safety testing may be considered for products containing live viruses, inactivated viruses, Gram positive killed bacteria, and spirochetes. In addition, dried antibody products that are administered by the oral route will be considered. Products that are “fall-outs” of larger combinations are eligible for consideration of an exemption to target animal safety testing based on an exemption for the parent product. Firms should initially submit one product exemption request to the reviewer. Once the necessary submissions and data have been reviewed and accepted for the initial product, additional exemption requests from the firm may be considered.

Initial submission to request exemption to target animal safety testing

1. A report should be included with the initial request for an animal safety testing exemption. The report should provide an overall assessment of the product’s safety performance. The following items should be included in the report.
 - a. The number of serials manufactured
 - b. The number of years the product has been on the market
 - c. The number of doses sold
 - d. The pharmacovigilance history (within dating period when serials were available for field use), including the frequency and seriousness of any adverse reactions in the target animal species, together with a discussion and/or justification of the likely causes of these events. Firms should reference VSM 800.204 for guidance regarding adverse event reporting.
 - e. Sterility and animal safety testing results; Results of the last 10 consecutive serials as specified in Section V.A. and V.B of the Outline of Production (purity and safety results). At least half of the consecutive serial data must include safety tests conducted with host animals at or below minimum age. A minimum time span might also be appropriate for certain products.
 - f. A summary of all approved production changes made since licensure and during the timeframe the most recent 10 serials were manufactured.
 - g. The CVB-IC inspection reports covering the manufacturing period of the consecutive serials referenced in Section 1.e. will be reviewed. To expedite processing of animal safety testing exemption requests, it is acceptable for the firm to provide copies of these inspection reports. Otherwise, the reviewer may access

2. An updated Outline of Production that addresses Items a-g below, submitted with an APHIS Form 2015, should be included with the initial request for an animal safety testing exemption. The following items in the Outline of Production should be considered to determine if manufacturing processes are controlled. Appropriate revisions to the Outline of Production are required prior to approval of the exemption.
- a. Consistency in concentration steps: Adequate detail and specifications must be provided.
 - b. Consistency in antigen input: the firm should propose an upper antigen limit and provide justification. Lower limits must also be specified, and pre-inactivation titers should be considered for killed products.
 - c. Appropriate ranges must be specified for all critical steps and specifications (e.g. temperature, time, concentration, pH, volume)
 - d. Section V.A. sterility testing must be conducted in accordance with 9 CFR 113.26 for all products. 9 CFR 113.27(a)(7)(ii) allows for growth in 1/10 test vessels in the initial test, or 19/20 vessels in the retest to meet satisfactory requirements. In order to be considered for an animal safety test exemption, if growth in any test vessel of the final test is observed, the serial should be considered unsatisfactory, as per 9 CFR 113.26(c)(3). If the sterility test is valid, for example in the case of a justified “no test,” a retest may be allowed. Other than that, no sterility retests will be allowed for products considered for the animal safety testing exemption. Supplemental Assay Method 908 provides guidance regarding how to conduct 9 CFR 113.27(a) sterility testing. Sterility retests may nullify the animal safety testing exemption.
 1. For oral antibody products; identification of contaminants is also required.
 2. The approval date of dilution of preservative studies must be provided in Section V.A.
 3. Media used in sterility testing should be validated for growth promotion as per 9 CFR 113.25(b) or an approved exemption should be documented in the Outline of Production.
 4. In general, if 3 consecutive serials, or 3 serials within a short period of time yield unsatisfactory sterility results, the animal safety testing exemption may be nullified for the product, unless acceptable justification based on mitigating circumstances is provided.
 - e. The Outline of Production must include methods to ensure confirmation that the adjuvant is sterile.
 - f. For inactivated products, the methods describing the inactivation check test must be specified in detail in Section IV. The test method must be determined to be adequate.
 - g. Confirmation of dating approval must be provided in Section VI.C.

Documentation of the Target Animal Safety testing exemption

The target animal safety testing should remain in Section V.B of the Outline. After the exemption is approved, the date the exemption was approved should be added to the Outline

of Production. The target animal safety tests that the firm should perform if the exemption is suspended for any reason should remain in the Outline of Production.

Maintenance of the Target Animal Safety testing exemption

To facilitate tracking of serials of target animal safety exempted products, the Remarks section of the 2008 for each serial should indicate that the serial is exempted from target animal safety testing. [REDACTED]

[REDACTED] In order to maintain the target animal safety testing exemption, pharmacovigilance monitoring should occur and reports with updated safety profiles should be submitted to the reviewer every 12 months. According to 9 CFR 116.5(b), immediate notification is required “if at any time there are indications that raise questions regarding the purity, safety, potency, or efficacy of the product. The reviewer should be cced on these immediate notifications for animal safety exempted products. The reporting interval may be revised based on data received initially, or later. If data received provides any indication at all that there might be safety issues the exemption should be nullified.

Exemption Nullification and Re-Issuance

[REDACTED]

[REDACTED]

[REDACTED]