



## VS Memorandum (VSM) 800.127

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### Guidelines for Conducting Product Stability Studies

#### 1. Purpose and Background

This memorandum provides guidance for studies intended to support the stability criteria of biological products. It recommends certain aspects of stability study design that the Center for Veterinary Biologics (CVB) recognizes as important. It also applies to products administered to animals; it does not apply to veterinary diagnostic products.

Title 9, *Code of Federal Regulations* (9 CFR), [114.13](#) requires establishment of a dating period for every veterinary biological product in accordance with the stability of each of its fractions. This document communicates the CVB's general approach to the concept of product stability and provides guidance for designing and conducting stability studies.

#### 2. Document Status

- A. Issue Date: 03/04/2021
- B. This is a new document. This memo is intended to help further clarify 9 CFR [114.13](#) published in March 2018.

#### 3. Authority and References

##### A. Authorities

- [9 CFR 101.5](#)
- [9 CFR 113](#)
- [9 CFR 114.13](#)

##### B. References

- [VSM 800.112](#), Guidelines for Validation of In Vitro Potency Assays
- [VSM 800.124](#), Guidelines for Potency Specifications of Biological Products Administered to Animals
- [CVB Data Guide](#)

##### C. Definitions

- *Confirmation of dating*: In this document, the terms confirmation of dating (COD) study and stability study will be used interchangeably.
- *Potent or potency*: Relative strength of a biological product as determined by test methods or procedures as established by the Animal and Plant Health



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Inspection Service (APHIS) in Standard Requirements or in the approved Outline of Production for such product.

- *Potency degradation profile*: The potency degradation profile is the mathematical relationship between time and the potency of a product.
- *Practical standard deviation (PSD)*. The PSD is intended as a measure of the variability of the potency due to manufacture and testing.
- *Stability*: Stability refers to the effect of time on the relevant qualities of a product stored under specified conditions. This document deals with the stability of a product's potency.
- *Stability-indicating assay*: A stability-indicating assay is a validated quantitative analytical procedure that can detect changes over time in a pertinent property of the product.

### 4. Audience

VS employees and members of the biologics industry.

### 5. Guidance

#### A. Preliminary Stability Criteria

The stability criteria are the length of the dating period, the potency specification throughout dating, and the potency specification at release. The stability criteria are related to each other by the potency degradation profile. Before the COD study is completed, set preliminary criteria as follows. Setting preliminary potency specifications may also be necessary if a major change is made to the potency test (e.g., the measure of potency changes).

#### 1. The length of the dating period.

The firm shall propose a dating period for the product based on preliminary information available about the stability of each of its fractions. In the absence of such preliminary information, products will typically be assigned an initial dating period of twenty-four (24) months for nonviable products and eighteen (18) months for products intended to replicate in the host animal. The dating period is then confirmed or possibly modified based on the COD study. Subsequent changes to the dating period may be requested when supported by a stability study. Generally dating up to thirty-six (36) months will be considered. Products that are licensed prior to confirming the dating period must include a statement in Section VI.C. of the Outline of Production that dating has not been confirmed and that appropriate data are being collected.



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2. The specifications for potency throughout dating.

Set the throughout-dating specification(s) in accordance with [VSM 800.124](#) or in accordance with 9 CFR Standard Requirements for the fraction. The throughout-dating potency specifications are the minimum requirements for potency when tested at any time within the dating period. They are based on the pivotal potency (potency of the serial used in the pivotal efficacy study) and the PSD.

3. The specification for potency at release.

Set the release specification(s) in accordance with [VSM 800.124](#) or in accordance with the 9 CFR Standard Requirements for the fraction. Set the preliminary release specification(s) higher than the throughout-dating specification to account for potential potency loss during the length of the dating period. Base the difference between the two specifications, release and throughout-dating, on information available about the anticipated loss of potency for each fraction for the proposed dating period of the product. Release potency specification(s) will be necessary before completing the initial COD study.

### B. Stability Study Requirement

The stability criteria of each fraction of each product shall be confirmed or modified based on the results of a stability study. An initial stability study is necessary to confirm product dating but may result in changes to the release and throughout dating potency specifications. A stability study may be required when there is a major change to the product's composition, manufacturing method, or potency test that is likely to impact product stability or to support changes to the stability criteria.

### C. Stability Study Design and Analysis

1. Protocol

Submit a protocol prior to initiating any stability study. Submit the initial COD study protocol prior to licensure.

2. Test articles

Use a minimum of three (3) serials for each product code produced in a manufacturing facility according to the Outline of Production. For product lines, use a minimum of three (3) serials of the largest combination and at least one (1) serial from each fallout product. Create each serial from a different lot of bulk antigen (e.g., Lot A, Lot B, Lot C) for each fraction. When initial potency testing is conducted on final containers, select final containers of production serials for the study using a defined, documented process. Fully describe the process in a protocol prior to study initiation. Use the same serials for all fractions for the



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initial stability study. There may be instances in subsequent stability studies where it is not necessary to test all fractions on all serials.

In those instances in which the use of a stability-indicating assay is not required (9 CFR [114.13 \(d\)](#)), at least one (1) serial in the stability study should be batched near the minimum according to Section IV. I. of the Outline of Production.

### 3. Number of tests

The number of potency tests conducted on each fraction of each serial at each time point should be no less than that required for serial release according to the Outline of Production (e.g., if three (3) vials are tested for serial release, no fewer than three (3) vials should be tested at each time point in a stability study).

### 4. Initial test

The first test in the sequence shall be as close as practical to the day of filling into final containers or the date of final formulation if the potency of the product is tested in bulk form. The report and electronic data should indicate whether final containers were or bulk material was tested.

### 5. Subsequent tests

Conduct all remaining potency tests on material obtained from final containers. The number of final containers tested for each serial should be no fewer than that required for serial release as specified in the Outline of Production. The CVB recommends, but does not require, conducting testing of different serials on different calendar days.

## D. Stability-Indicating Assay

Stability studies must be conducted with a stability-indicating assay except those instances specified in 9 CFR [114.13 \(d\)](#).

### 1. Quantitative and quantal assays

Quantitative potency assays such as one that produces a live bacterial count, or a quantal assay such as a live virus titration, will be considered stability indicating if the test method has been validated in accordance with [VSM 800.112](#). Additional test methods validated according to [VSM 800.112](#) that quantify the concentration of the sample may be considered quantitative (and hence stability indicating) as well.



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### 2. Relative potency assays

Relative potency assays validated in accordance with [VSM 800.112](#) Appendix III will be considered stability indicating if the same reference is used for all testing during the stability study and no critical reagents (e.g., capture antibody, detector antibody, etc.) have changed during the stability study. If a reagent is nearing depletion, the firm may save sufficient quantity to finish the stability study even if the reagent is replaced for routine serial release. The initial test should be planned so that the reference remains in-dating for the length of the stability study.

### 3. Dichotomous outcome animal tests

Animal tests that provide only a dichotomous (satisfactory/unsatisfactory) outcome (such as eight (8) of ten (10) lab animals meeting a requirement) are unsuitable to test potency for a stability study except for the exceptions listed in 9 CFR [114.13 \(d\)](#).

### 4. Other in vivo tests

An *in vivo* potency test that measures a response in the laboratory animal model that is related in a dose-responsive manner to efficacy in the target species and the product's antigen concentration may be considered stability indicating.

## E. Analysis for In Vitro Assays

Analyze the data to obtain a final estimate of the mean potency loss (MPL) and verify the appropriateness of the PSD.

### 1. Model

Fit a suitable regression model to the potency values obtained from testing of final containers to describe the potency degradation profile. When appropriate, use the logarithm of the potency estimates as the response variable in the regression model. Use a linear regression model when the degradation rate is fixed. Use a nonlinear regression model when the degradation rate is time dependent. When degradation cannot be distinguished from assay and vial variability, use an intercept only model.

### 2. Final PSD

PSD may continue to be used if the estimate of root mean square error (RMSE) from the model fit to the data from the stability study does not exceed 3 x PSD. If the RMSE exceeds 3 x PSD, there is an indication the PSD estimate is too low to appropriately account for all sources of variation. In such instances, the PSD will



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need to be reevaluated or the throughout-dating specification can be adjusted using RMSE in place of PSD.

### 3. Final MPL

Use the appropriate regression model to determine the expected amount of potency decline when stored in final containers during the dating period. The potency decline is determined as the difference between the potency estimated from the regression model at time 0 and at the time equal to the proposed dating period (e.g., eighteen (18) months). Alternatively, the difference between the preliminary release and throughout-dating specifications along with the observed mean potency loss through time can be used to determine the dating period.

### 4. Submission to CVB

Submit a report describing the study design, analysis, and final conclusions to the CVB. Include all raw data and calculated potency test results in accordance with the [CVB Data Guide](#). Submit reports within eight (8) months of the final potency test. If Option 3<sup>1</sup> ([VSM 800.124](#)) is selected and the product is licensed prior to the completion of the COD study, the COD must be completed no later than the date of licensure + product dating + eight (8) months.

## F. Monitoring Stability of the Product

As described in 9 CFR [114.13 \(i\)](#), product stability must be monitored for products licensed after April 13, 2018. Test three (3) percent of serials produced in a calendar year with a minimum of one (1) serial and a maximum of three (3) serials. For determining the number of serials, all subserials can be classified as the same serial. All serials tested for monitoring should be unique (i.e., not different subserials). Each of these serials should be tested within thirty (30) days of expiration to monitor the stability of the product. For product lines, only the largest combination needs to be tested. Submit a monitoring plan to the CVB that describes how serials will be selected for monitoring. It may be possible to use the same general plan for multiple products.

Submit all data (cumulative) every three (3) years for review. Results should be available for the CVB's review upon request.

## G. Implementation/Applicability

Updated policy as it relates to stability studies initiated after the date of the memorandum is effective immediately. Submit the stability monitoring plans and implement testing within one (1) year from the date of this memorandum.

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<sup>1</sup> Option 3 from VSM 800.124 requires testing 6 vials initially, after one month, and at expiration.