Guidance to Industry
Preparing Supporting Summaries for
Single Tier (Single Label Claim) Effectiveness Statements

Contents

I. Overview

As part of a movement in 2015 toward single-tier effectiveness statements, 9CFR 112.5(b) was amended to require publication of efficacy and safety study summaries on the APHIS website productdata.aphis.usda.gov. This document provides details to licensees, permittees, and applicants on preparing and submitting information for those summaries.

A summary of a single study is known herein as an Individual Study Summary (ISS). It is prepared by the licensee/permittee and reviewed/edited/cleared by the Center for Veterinary Biologics (CVB) for standard content and appearance. All of the ISSs applicable to a single biological product are then compiled into a Product Compilation Summary (PCS), which is posted to productdata.aphis.usda.gov. The compilation is performed by the CVB.

II. Scope of Products Affected by Single-Tier

Vaccines (including prescription platform products), bacterins, toxoids, and immunomodulators are included under the scope of the new rule.

Products exempted include: antibody products, diagnostic test kits, autogenous, and allergenic extracts.

III. Scope of Studies Requiring Single-Tier Summaries

1. Prepare Individual Study Summaries for the following:
   - Efficacy studies directly supporting licensure of a product
     - Host animal vaccination-challenge or field efficacy studies (short-term and duration of immunity): pivotal pre-license efficacy and any subsequent studies that change claims or instructions for use.
     - Host animal vaccination-challenge to establish immunogenicity for the addition of new influenza subtypes in licensed products per VSM 800.111.
     - Codified tests highly correlated to host animal efficacy, which the CVB allows as fulfillment of pivotal efficacy requirements for certain agents (e.g., *Clostridium tetani*, and select other *Clostridium* spp serology)
   - Safety studies
     - Routine field studies (VSM 800.204)
     - Additional safety studies to support specific claims (e.g., safe for use in pregnant animals).

2. Individual Study Summaries are typically *not* required for the following, unless specifically requested by the CVB:
   - Reasonable expectation of efficacy for a conditional license
   - Reference qualification studies that merely confirm the findings of prior pivotal efficacy
   - Backpassage or shed/spread studies

- Proof-of-concept efficacy studies or studies conducted solely to fulfill requirements for foreign registration
- Component compatibility studies other than host animal vaccination-challenge (e.g., serological non-inferiority)
- Overdose safety studies
- Residue clearance studies
- Studies for products solely for official/emergency use by APHIS

3. Full Individual Study Summaries are required for applicable studies submitted to the CVB on, or after January 1, 2007. Studies submitted prior to 2007 do not require a full summary, although one may be submitted voluntarily. Alternatively, a placeholder, as described in Section VI.C below, may be submitted. All product classes within the scope of single tier must have single-tier language on labeling, even if only placeholders are published on the CVB website.

IV. Individual Study Summary (ISS) Procedure

1. Use the ISS template provided by the CVB. Refer to the line-wise instructions provided in the following section for details on how to prepare the ISS. Submit the ISS to CVB as a Microsoft Word document to facilitate editing by CVB. Contact the CVB at CVB.Single.Tier@usda.gov if you do not have access to Microsoft Word software.

2. Submit ISSs for previously accepted studies as they are available. See the single tier implementation timeline for current goals for completion.
   - Co-submit an electronic copy of the historical study report if it was originally submitted as a paper copy. This will help the CVB expand its collection of digitized key documents.
   - If known, also provide the submission date and CVB mail log number of the original study.
   - Include a copy of the CVB acceptance letter if it is readily available, but latitude is given for letters that would be problematic to locate.

3. Submit ISSs for new studies after the study report has been accepted.

4. Please submit ISSs electronically, preferably using the NCAH Portal. For non-portal users, provide the submission electronically on a CD, DVD, memory stick, or other similar device. As a reminder, the device will remain with the CVB and will not be returned to the firm.

   Complete APHIS Form 2049 and include the Microsoft Word document of the ISS and additional related reports/letters as applicable. Use the following values on APHIS Form 2049 to clearly identify the submissions:
   - **Submission type**=Historical Study Summary
   - **Product Codes:** Enter all *current* product codes to which the study applies. Due to acquisitions, mergers, and the subsequent licensure of related products, the codes may

differ from those originally associated with the study. Justify the addition/substitution of codes that were not associated with the original study report.

- **Brief Description:** Indicate whether the submission is a full ISS or only a placeholder and other relevant information for the study
- **Attachment type** (NCAH Portal users only)**:** Use **Draft Individual Summary** to upload the ISS. Use **Incoming Document (Core)** for any other co-submitted documents. Add the study identifier to the report or the Draft Individual Summary.

5. ISSs will be reviewed for acceptable format, clarity, and consistency by the Single-Tier Implementation Team. The Team is a small group of reviewers who have developed expertise in ISSs. If any major revisions are needed, the CVB will maintain transparency with the submitter to generate an acceptable ISS.

6. Once the ISS is cleared for publication, the cleared version will be converted by the CVB to PDF, and a copy will be provided to the submitter for the firm's files. Firms will be given two weeks to contact the CVB at CVB.Single.Tier@usda.gov if issues with the cleared ISS are noted. This ISS may then appear in a Product Compilation Summary (PCS) for any applicable product.

V. ISS template

A. First page

The first page of the ISS template contains a table with identifying information that will not be included when this ISS is incorporated into a PCS by the CVB. PCSs will have their own cover page containing appropriate identifying information for the Product. To facilitate computerized assembly of the PCS by the CVB, the table on page 1 of an ISS template must be the only item on Page 1 of the completed document.

First page table:

Original Establishment Number	Enter the Est # from which the study was submitted, even if (as in the case of split manufacture or acquisition/merger) the study may pertain to another Establishment's final-use product
Original Product Code	Enter the original code(s) of the product under which the study was submitted.
Current Product Codes	Enter the *current* Est # if it is different from the original Est #. Enter any *current* codes to which the study applies. We realize this may not agree with the original code if the product has been subject to acquisitions and mergers.
Study Identifier	The CVB strongly encourages applicants to create a unique ID for studies. Enter the identifier, if one was created. The CVB recognizes there may not be a unique ID for certain historical studies.

Date Study Submitted	Enter the date the efficacy/safety study was submitted to the CVB (not the submission date for the Individual Study Summary if it is submitted after the study was reviewed)
CVB Mail Log ID containing study	For historical studies, the CVB Mail Log (ML) ID of the full study submission will differ from the ML assigned to the individual study summary because they are being submitted separately. In many cases, the ML ID assigned to the full study report may not be known to the firm. The CVB may add this information later if we can trace the ML # in our records. Some studies may pre-date any kind of CVB Mail Log.

B. Subsequent page(s)

The following table, to begin on page 2 of a completed ISS, will appear in PCSs.

Study Type	Enter Efficacy or Safety.
Pertaining to	• Enter the agent against which efficacy is being demonstrated. For influenza products, include the influenza strain by WHO nomenclature (e.g., A/California/04/2009(H1N1). • For BVD products, enter the type (e.g. Type 1, Type 2). • For PCV products, enter the genotype (e.g. 2). Enter ALL for safety studies.
Study Purpose	Be succinct and non-technical, using plain language. Examples: • To demonstrate efficacy against diarrhea in piglets nursing vaccinated sows • To demonstrate efficacy against respiratory disease one year after vaccination • To demonstrate safety under field conditions • To demonstrate safety in pregnant animals
Product Administration	Include the number of doses, interval between doses, and the route of administration. If the product administered is a platform product, include the identity of the inserted gene for the serial used in the study.
Study Animals	Include the animal species, age at first product administration, and number of animals per treatment group. For efficacy studies, the number of animals per treatment group should be the number included in the final study analysis. For field safety trials, all animals enrolled in the study should be represented. State an age range indicating the number of animals at the minimum age.

Challenge Description	Include the challenge agent and time interval between the last product dose and challenge. If the challenge agent is a generally recognized strain (e.g., Singer strain of BVD1 or Rickard strain of FeLV), please indicate it.) • Bovine Virus Diarrhea Virus-state the type, subtype, and strain. • Infectious Bronchitis Virus-state the type. • Infectious Bursal Disease Virus-state the type. • Influenza Virus-state the subtype and strain. Designate the strain according to accepted standards of influenza virus nomenclature. • Newcastle Disease Virus-state the strain. • Porcine Circovirus-state the type and subtype. • Rabies Virus-state the strain. Enter "Not applicable" for safety studies.
Interval observed after challenge	Specify how long, and how frequently, animals were monitored for safety studies and after challenge for efficacy studies.
Results	*****See the following section of this document for data formatting requirements.***** Efficacy: Focus on results that provided the primary basis for regulatory acceptance. Avoid myriad unremarkable secondary findings. Define any complex case definitions and indicate when the test was conducted according to a codified Standard Requirement. Explain scientific/medical terms in plain language. If multiple dose concentrations or different routes of administrations were tested, present only the data for the formulation/route that was approved for licensure. Safety: Account for all enrolled animals by adverse event observed. Presentation: If a table or graphical presentation does not fit easily in the Results block of the ISS template, append additional pages to the template and refer the user to the added pages. If the data fit better on 8.5 x 11" pages in landscape view, it is permissible to rotate the data sideways on portrait-oriented pages. (Example ISS #9 contains rotated text.) Do not rotate individual pages within the Word document, however, as this creates problems during the CVB's automated compilation of a Product Compilation Summary.

	If data were presented in tabular format in the study report, the same table may be copied/pasted into the ISS, provided there is adequate resolution to retain readability.

VI. Data Requirements

Example ISSs for a variety of study designs are available on the CVB website. These are not meant to reflect the *only* way that study data can be presented, but they do provide acceptable examples. All presentations of study data must meet the following guidelines:

A. Efficacy Studies

1. Raw data: All efficacy ISSs must present *raw* study data. The ISSs are intended to meet the needs of a wide variety of readers.

Strive to present raw data in a meaningful, concise manner, but do not combine/collapse data so that information is lost.

- Example: In example ISS #1, it would have been inappropriate to reduce the data for each calf to an overall yes/no outcome, as there were two parameters (virus and antibody) being evaluated. Information about individual calves would have been lost if those findings were combined into a single composite outcome.

2. Summarizations: *Limited* high-level summaries are permissible, but not required, to accommodate readers who do not wish to examine raw data. The following types of summarizations are allowed *in addition to* raw data:

- 5-number summaries are allowed for continuous numerical data, such as lung lesion scores or the duration of an event. Example ISS #5 shows this type of summarization.
- Totals are allowed for dichotomous or qualitative data, such as total mortalities or the number of animals meeting the criteria of a multi-factorial case definition. Express totals as the number affected over the total number (e.g., 9 of 25 died). Similarly, percentages are also allowed as long as the numbers are included (e.g. 9 of 25 (36%)).
- It is permissible to include a "final classification" column at end of raw data to show the disposition for each animal (positive or negative). Example ISS #7 illustrates this type of summarization.

Do not include other summarizations, such as averages or means. Do not include statistical analyses, such as prevented fractions or p-values.

B. Safety Studies

For field safety trials (FST) according to VSM 800.204, a tabular presentation is recommended. The presentation may be in one or more tables to present the data adequately.

1. Account for every animal enrolled in the study. For the FST ISS, an animal is considered enrolled once it has received the first vaccination. Indicate the number of animals that completed the study (with or without an adverse event (AE)) and the number that did not complete the study (with or without an AE). In some circumstances it may be acceptable to provide this information in narrative form rather than in a table.

2. Present a table listing the AE by category.
    - The number of AEs may not match the number of animals experiencing AEs, since an animal may experience more than one AE.
    - AEs that are *clearly* considered to have a plausible cause other than vaccination may be included in a separate category. (Example: An animal dies a few days after vaccination due to accidental trauma). The explanation must be in the study report with adequate justification (i.e., definitive data) to rule out vaccination. Such AEs may be indicated as "affirmed by licensee to have a cause other than vaccination." Example **ISS #15** shows this type of summary.
    - Explanatory notes may be included to indicate circumstances that may affect the interpretation of the observations or where there is not a sufficient degree of certainty to designate the AEs as having a cause other than vaccination. In that case a short, concise explanation may be provided below the table. (Example: Pigs vaccinated with a *Mycoplasma hyopneumoniae* bacterin are part of a herd that experiences an influenza outbreak a couple of days later.) Example **ISS #16** shows this type of summary.

3. Where appropriate, present a table of injection site swelling. Tabulate local injection site swelling by size and duration. Example **ISS #10** shows this type of summary.

4. For poultry studies, include data for mortality, hatchability, and condemnation as required or on a case-by-case basis. Hatchability data are required for products administered *in ovo*. If the data are not available, make an explanatory notation. Mortality, hatchability, and condemnation data may be presented as percentages as long as total animal numbers are reported. Example **ISS #14** shows this type of summary.

C. Exceptions for Historical Studies

The data requirements described in Sections V.A and V.B are expected for all summaries for studies conducted in 2017 forward. It is highly likely that studies of the past several years also will have the detail necessary to meet these requirements. The CVB recognizes that some older study reports may not have the detail necessary to meet all of the summary

requirements, and these will be handled on a case-by-case basis to best present the available data.

If a full ISS will not be submitted for a study conducted prior to 2007, submit a placeholder ISS instead. Follow the format shown in ISS Example #17.

VII. Product Compilation Summaries (PCSs)

All of the ISSs for a given product are appended together to create a PCS. The compilation is a computerized process performed by CVB data systems. An example PCS is on the CVB website.

A courtesy copy of each PCS is then sent to the firm. Firms are asked to provide any feedback on errors to cvb.single.tier@usda.gov within 2 weeks. Since the PCSs are merely a grouping of previously cleared ISSs, errors/concerns should be rare.

- PCSs for new products will be generated and sent to the firm at the time of product licensure. There will be a delay of at least 28 days before posting the PCS to the productdata.aphis.usda.gov website. Firms wishing to have a PCS posted earlier than 28 days after licensure can request an earlier date by emailing **cvb.single.tier@usda.gov**. (Do not email your firm's reviewer.)
- PCSs for currently licensed products may be sent to the firm at any time after all of the component ISSs have been cleared and at least 28 days prior to posting the PCS on productdata.aphis.usda.gov.
- If a product is licensed and the PCS has not yet been published on productdata.aphis.usda.gov, firms may distribute their copy of the PCS, without alteration or embellishment, to interested parties.
- Updated PCSs may be generated if an eligible study is conducted after initial product licensure.
- French versions of published PCSs may be considered for publication if approved and submitted by the Canadian Food Inspection Agency (CFIA) to the CVB. Licensees and permittees should consult with CFIA when PCS revisions are needed to ensure consistency with the CVB generated PCS.

VIII. Updating Product Codes Associated With Approved ISSs

Licensees and permittees may need to update the list of product codes associated with a cleared (approved) ISS. When this occurs, use the following process:

- Do NOT resubmit the ISS.
- Make a formal submission with the following parameters:
  - Submission type=Historical Study Summary
  - Brief Description="Request to update product codes associated with previously cleared ISS"

    - Related Submissions = ML of submission where ISS was processed
- Attach a justification for each code addition

The CVB will evaluate the request. If eligible, a new ISS with only the newly requested product code(s) will be generated by the CVB based on the previously cleared (approved) ISS, and then returned under the new submission. The previously cleared (approved) ISS will not be changed. If the codes are not eligible to be added to a previously cleared (approved) ISS, the request will be denied.