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VS Memorandum 800.125

Preparation and Submission of Adverse Event Reports for Biological Products by Licensees and Permittees

1. Purpose and Background

The Center for Veterinary Biologics (CVB) is issuing this memorandum to provide guidance to all licensees and permittees on preparing and submitting adverse event reports to Animal and Plant Health Inspection Service (APHIS) Veterinary Services (VS). This guidance ensures reports meet the intent of the regulations, as specified in the recently updated regulations included in title 9, *Code of Federal Regulations* (9 CFR), 116.9. Adverse event reports submitted to licensees and permittees are an important part of CVB's mission to ensure that veterinary biological products are in compliance with the Virus-Serum-Toxin Act.

The Virus-Serum-Toxin Act regulations concerning records and reports, as specified in 9 CFR 116.9, require veterinary biologics licensees and permittees to record and submit reports concerning adverse events associated with the use of the veterinary biological products they produce and distribute. These records and reports will assist VS in monitoring the performance of licensed veterinary biological products over time. This allows VS to provide complete and accurate information to consumers regarding adverse events or possible concerns associated with the use of these products. Adverse event report records are maintained for a period of three years after the adverse event is received. Adverse event reports determined by the licensee or permittee to be product-related, serious, and unexpected must also be reported immediately. All other adverse events must be reported within 90 calendar days of the date the report was first received. APHIS amended the definitions in 9 CFR 101.2 to define adverse events and adverse event report.

The regulations regarding adverse event reporting went into effect June 18, 2018. However, CVB Notice 18-09, "Implementation Period for the Submission of Adverse Event Reports," posted on June 25, 2018, explains that there is an eighteen (18) month minimum phase-in period for the implementation of the regulations, during which CVB will not require licensees and permittees to submit adverse event reports as described in 9 CFR 116.9.

Pursuant to the Congressional Review Act (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as a non-major rule, as defined by 5 U.S.C. § 804(2).

2. Document Status

A. Issue Date: 08/17/2020.

B. This is a new guidance document.

3. Authority and References

A. Authorities (*Code of Federal Regulations* (CFR)):

- 7 CFR 371.4
- 9 CFR 101.2
- 9 CFR 116.9

B. References

- CVB Notice 18-09

C. Definitions

1) **Adverse Event:** Any observation in animals, whether or not the cause of the event is known, that is unfavorable and unintended, and that occurs after any use (as indicated on the label or any off-label use) of a biological product, including events related to a suspected lack of expected efficacy. For products intended to diagnose disease, adverse events refer to a failure in product performance that hinders an expected discovery of the correct diagnosis.

2) **Adverse Event Report (AER)**: Direct communication concerning the occurrence of an adverse event from an identifiable firsthand reporter which includes the following information:

a) An identifiable reporter;

b) An identifiable animal*;

c) An identifiable biologic product; and

d) One or more adverse events.

Note: Report all AERs for VS licensed/permitted product distributed within domestic and/or international markets.

*Where specific information regarding an animal's identity is not readily available, CVB will consider the species for which the product was used to be the minimum information for an "identifiable animal."

3) **Marketing Authorization Holder (MAH)** The MAH is the licensee or permittee who is responsible for the pharmacovigilance of the licensed or permitted biological product.

4) **ABON System:** The ABON system is the acceptable method used for assessing causality and categorizes adverse events into five (5) main categories, which are as follows:

   Probable (A) Possible (B) Unclassifiable (O) Inconclusive (O1) and Unlikely (N).

   a) Category A: **Probable** - *All* of the following minimum criteria apply:

      i. There should be a reasonable association in time between the administration of the biological product and onset and duration of the reported adverse event.

      ii. The description of the clinical event should be consistent with, or at least plausible, given the known ingredients of the biological product described in the adverse event.

      iii. There should be no other equally plausible explanation(s) of the case reported.

   b) Category B: **Possible** - The administration and/or use of the biological product is another possible and plausible cause for the reported adverse event where the available data do not meet the criteria for inclusion in Category A.

   c) Category O: **Unclassifiable/Unassessable** - Applied to cases where reliable data is unavailable or insufficient to make an assessment of causality.

   d) Category O1: **Inconclusive** - Associative other factors prevented the assessor from drawing a definitive conclusion regarding causality (A or B), but in which association cannot be discounted.

   e) Category N: **Unlikely -** Sufficient information exists to establish beyond a reasonable doubt that the adverse event described in the AER was not likely due to the use of the veterinary biological product.

5) **Serious Adverse Event:** Any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect.

6) **Unexpected Adverse Event:** An unexpected adverse event is an adverse event of which the nature, severity, or outcome is not consistent with VS-approved labeling for licensed or permitted products distributed within the United States or filed Outlines of Production.

7) **Product-Related:** The submitter has assessed causality to be probable or possible according to the ABON causality assessment classification system. For individual AERs, the ABON classification of probable or possible does not indicate that the

MAH has established a causal link for any or all clinical signs reported with the adverse event.

8) **Causality Assessment:** Each MAH or licensed or permitted distributor (refer to Section A.2 below) will make a determination as to whether the adverse event(s) described in an individual AER is/are related to the MAH's biological product(s) identified in the AER. For the purposes of reporting adverse events to CVB under 9 CFR 116.9, the "ABON system" is the acceptable method to use for assessing causality for each product the firm is responsible for reporting.

9) **Veterinary Dictionary for Drug Related Affairs (VeDDRA) Terminology:** A list of terms for reporting clinical signs in suspected adverse events in animals and humans to veterinary medicinal products, of which veterinary biological products are included.

10) **Gateway**: A dedicated and secure transmission portal that allows licensees and permittees to electronically transmit either single or batch AER cases in xml file format to CVB, with subsequent importation of these cases into the CVB pharmacovigilance databases.

4. Audience

VS employees, licensees and permittees.

5. Guidance

A. MAH Responsibilities and Requirements

1) Implement a documented process to ensure AERs are captured, thoroughly assessed, appropriate action taken as required, and reported to CVB in compliance with the regulations.

2) The MAH that holds the license or permit for the biological product identified in an AER is ultimately responsible for the accuracy, quality, and actions taken as a result of the AER submitted to CVB for the product. Third parties or distributors are not authorized by VS to submit AERs on behalf of the MAH unless the distributor is a licensee or permittee and the MAH agrees with this arrangement.

3) A primary pharmacovigilance contact must be identified for the MAH. An APHIS Form 2007 must be submitted to CVB with the role of Consumer Complaint Contact (CCC) selected. The MAH may not submit AERs to CVB or obtain guidance and instructions for XML file format submissions of AERs until the CCC has been identified by the MAH and the APHIS Form 2007 for this individual has been received and processed by CVB. Up to four CCCs may be identified per licensee or permittee.

B. Methods to Initiate and Submit AERs to CVB

1) Licensees and permittees must report individual AERs to CVB using one of the two methods listed below to maintain compliance with 9 CFR 116.9:

   a) Gateway: Transmit AERs generated in XML file format electronically through the Gateway. Use of the Gateway is not limited to the number of cases to be submitted, or the type of pharmacovigilance information gathering systems used, as long as CVB-supplied user guidance is followed (see Section B.2.a).

   b) PV Express II: The PV Express II electronic adverse event reporting form for industry is located on the CVB website: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event

2) Guidance and instructions for preparing and submitting AERs can be accessed by:

   a) XML File Format Transmission: CVB epidemiologists will provide specific AER formatting and onboarding guidance instructions for transmitting AERs using the Gateway to guide the submitter in initiating these XML submissions. Firms using this method must contact the CVB epidemiologists to obtain specific user guidance. The CVB preferred method of contact is by using the following email address: CVB.Pharma@usda.gov

   b) Web Based Transmission: Guidance and instructions for submission of AERs using PV Express II can be accessed at: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event

C. Preparing Adverse Event Reports for Submission to CVB

1) AER content: The information requested for each AER follows VICH Guidelines 24 and 42. For more information visit: https://www.vichsec.org/en/guidelines/pharmacovigilance/vich-gls-24-29-35-42.html

2) Information to report to CVB: All fields identified in the guidance document for Gateway XML submissions and the PV Express II online form if this information is known.

3) VeDDRA Coding: VeDDRA coding using VeDDRA terminology for each clinical sign reported as part of completing an AER for submission to CVB must be performed. Guidance for VeDDRA coding can be found at the AER page of the CVB website https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event

4) Find further guidance regarding preparing AER submissions in the Appendix: Additional Instructions for Preparing and Submitting an AER.

D. Frequency for Reporting Adverse Events to CVB

1) The required frequency for submitting AERs to CVB is as follows:

   a) **Immediate reporting:** Adverse events that are serious, unexpected, and product related must be submitted immediately to CVB and must occur within three (3) business days from when the submitter makes the determination these criteria apply. However, the total time to make an immediate submission to CVB must not exceed fifteen (15) business days from the date when the report was first received. Refer to the Appendix, item 1) for further information.

   b) **Periodic reporting:** Report adverse events not requiring immediate reporting, as described in Section D.1.a above, to CVB within ninety (90) calendar days of when the submitter first receives an individual report.

   c) **Follow-up adverse event reports:** Submit follow-up reports to CVB within fifteen (15) business days of verifying the follow-up submission as complete. Identify follow-up submissions with the appropriate case number from the original submission.

E. Reporting Distribution to the Marketplace

1) Annually provide doses/tests (for diagnostic test kit products) distributed to the marketplace, by country, for each biological product for the twelve (12) months preceding the end of each calendar year. Supply this information within sixty (60) calendar days after the end of the calendar year. It is not necessary to provide this information for products that have not had any AERs reported to the licensee or permittee during the above referenced time period.

2) For circumstances including, but not necessarily limited to, conditional license requirements and other CVB-directed requests for periodic adverse event reporting (for example, quarterly AERs) provide the doses/tests to the marketplace, by country, for the time period specified in the CVB request.

F. Implementation/Applicability

Updated policy in this memorandum is effective six (6) months after the Issue Date listed in Section 2.A

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Appendix: Additional Instructions for Preparing and Submitting an AER

The following is not an all-inclusive listing, but rather some key items to consider when preparing AERs for submission to CVB:

1. For AERs submitted in accordance with 9 CFR 116.9(b)(2) and 116.9(b)(3), the original receipt date is the date of first receipt of information by the submitter responsible for reporting the AER to CVB. CVB interprets receipt of information to include the following four (4) data points:

   a) An identifiable reporter;
   b) An identifiable animal;
   c) An identifiable biologic product; and
   d) One or more adverse events.

2. The date remains the same for follow-up or future submissions concerning an AER. CVB expects each submitter to perform due diligence to obtain the four (4) data points noted above when initially obtaining information from the reporter.

3. Provide the correct establishment and product code number as assigned by CVB for each biological product that the submitter is responsible for reporting.

4. For AERs involving human exposure to a biological product, report only symptomatic human exposures to CVB.

5. Each report of an adverse event must provide VeDDRA terms for each of the clinical signs described in the case narrative. CVB will use the latest version of VeDDRA terms; however, CVB will also accept the previous three (3) versions of VeDDRA. Guidance for VeDDRA coding can be found at the AER page of the CVB website: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event

6. Adverse event reports submitted for diagnostic test kit products should not include issues related to technical errors or equipment failures.

7. For VeDDRA coding of diagnostic test kit products use “unclassifiable adverse event” as the only VeDDRA term.

8. Do not report product defect issues to CVB as an adverse event if such issues are not associated with an adverse event as defined in Section C.1 above. Product defect issues may include, but are not limited to: Labeling errors, particulates observed in final containers, dented vial caps, or product color changes.

9. Consider initiating more than one (1) AER in instances where multiple animals are involved and multiple clinical signs reported. For example, if two (2) dogs are identified

in one (1) adverse event, and one (1) has an injection site reaction while the other dog has lethargy and vomiting, report these as two (2) separate adverse events.

10. Do not identify or submit AERs as immediate reports under 9 CFR 116.9 or identify as expedited/three- (3-)day alerts in an AER submission, regardless of the actual submission time-frame, that do not meet the three (3) criteria of being serious, unexpected, and product related.

11. Each submitter should exercise due diligence to obtain and report the correct serial number for each biological product identified in an AER. However, CVB knows the primary reporter may not always provide this information. In this case, use the term "unknown" in place of the serial number.