OFFICE OF SURVEILLANCE AND COMPLIANCE

REVIEW AND ASSESSMENT OF POST-MARKET ADVERSE DRUG EXPERIENCE DATA

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I. PURPOSE

Each applicant of an ANADA (Abbreviated New Animal Drug Application) or NADA (New Animal Drug Application) must submit Adverse Drug Experience reports (ADEs) and Drug Experience Reports (DERs) in compliance with 21 CFR 514.80. An applicant of a conditionally approved product (CNADA) is also required to submit ADE reports and DERs in compliance with 21 CFR 514.80 as part of the conditions of the conditional approval. FDA reviews these records and reports to assess the post-approval safety and effectiveness of an approved application. This document establishes policy concerning FDA's assessment of these reports submitted under 21 CFR 514.80.

II. POLICY

FDA staff in the Center for Veterinary Medicine (CVM) regularly examine the CVM adverse drug event database as part of routine safety monitoring. FDA's review of ADEs received in compliance with 21 CFR 514.80 is completed through a tiered system that prioritizes review of recently approved and marketed products to establish post-approval safety reporting profiles. Established products continue to be assessed periodically throughout their lifespan for any unexpected changes to their post-approval safety reporting profiles.

All ADEs received by FDA involving reports of human exposure have priority review regardless of tier status of the approved application.

III. RESPONSIBILITIES

The Division of Pharmacovigilance and Surveillance is responsible for the procedures described in this document.

IV. DEFINITIONS

A. Tier 1 products

A newly approved animal drug is considered a Tier 1 product for at least 24 months after its approval* and subsequent marketing, if any of the following applies:

- the product is a new molecular entity**

- the product is a novel combination of existing or new molecular entities
- the product is an existing molecular entity (or combination thereof) approved in a new species
- the product is an existing molecular entity approved for a new route of administration

*Approval may refer to that of an original or supplemental application, including conditional approvals.

** New molecular entity refers to a molecular entity that has not previously been approved by the FDA for use in any non-human animal species.

Additionally, the Division Director or a Branch Chief within the Division of Pharmacovigilance and Surveillance may determine that a newly approved and marketed product that does not meet the above definition requires designation as Tier 1 status (e.g., pre-approval safety information is suggestive of a concern unique to the new product compared to similar previously approved products). All conditionally approved products are treated as Tier 1 products for the duration of the conditional approval.

B. Non-Tier 1 products

All other approved ANADAs or NADAs which are actively marketed that are not designated Tier 1 are considered non-Tier 1 products. Non-Tier 1 products include all generic products, as well as pioneer products that have been marketed for at least 24 months and have established adverse event profiles.

C. Signal detection and evaluation

A signal, for the purposes of this document, is defined as information that arises from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an adverse event or set of related adverse events, that is judged likely to justify further investigation to verify (e.g., use of causality assessment tools). New aspects of a known association may include changes in the frequency, distribution (e.g., age, breed), severity, or outcome of an adverse reaction.

Signal detection may involve the review of individual spontaneous adverse event reports, the use of statistical analyses (e.g., disproportionality analysis), or both. Signals can arise from several data sources, including all scientific information from the use of the veterinary drug product (e.g., quality, non-clinical, clinical, and post-marketing data), however, the scope of this document is generally limited to post-marketing data, primarily spontaneous adverse events reported in association with administration of a veterinary drug product.

Signal evaluation involves case series examination of cases contributing to the signal, as well as any other cases that may be considered relevant (e.g., cases with related terms), to assess for trends suggestive of a causal association between the veterinary drug product (and in some cases related drug products) and the adverse event(s). Other data sources (e.g., peer-reviewed literature for clinical and observational data, DERs, veterinary drug manuals, available pre-clinical data, information from other

regulatory authorities) are also examined for information regarding the association between a veterinary drug product and adverse event.

Conclusions from signal evaluation fall into the following categories:

- No action indicated – Available evidence is not suggestive of a causal association
- Monitoring – Available evidence may be suggestive of a causal association but is considered not sufficient to move forward with remedial action
- Action indicated – Available evidence is suggestive of a causal association and is considered sufficient to recommend remedial action.

V. PROCEDURES

A. Tier 1 products

A designated veterinary safety reviewer is assigned to an individual Tier 1 product at the time of its approval and generally continues to review that product until it transitions to non-Tier 1 status. Products are assigned to veterinary safety reviewers based on pharmaceutical class and/or indicated species.

ADEs received for Tier 1 products are routinely assessed by the assigned veterinary safety reviewer for possible causal association for at least the first 24 months after the product becomes actively marketed. Assessment of causality includes consideration of the timing of the ADE in relation to product administration, known association(s) of an ADE with the product (e.g., labeled sign, known reaction of product in another species, known reaction of closely related product(s)), rechallenge, dechallenge, and other possible etiologies (e.g., concomitant products/conditions) when this information is provided in the case narrative.

Every six months, a periodic safety assessment is completed to quantitatively describe the ADE profile of a Tier 1 product. Periodic safety assessments include, but are not limited to, clinical sign frequencies with reporting rates for all approved species, as well as for product defect and medication error cases, human exposure cases, and cases received for unapproved species. The periodic safety assessment may also include disproportionality analysis depending on the case volume of an individual Tier 1 product. Identified signals from these processes are further assessed by signal evaluation.

After initial signal evaluation, safety signals identified by the safety reviewer as potentially requiring remedial action are brought to the attention of and discussed with the Branch Chief. At this stage, it may be determined that safety signals require further evaluation and/or remedial actions are identified. Information regarding the safety signal and proposed remedial action(s) is communicated to the ONADE target animal review division. Further discussion between the Offices may occur depending upon the complexity of the signal and proposed remedial actions.

Post-Approval Experience (PAE) sections on the product insert are intended to convey information to the veterinarian or other end-user regarding the safety profile of the veterinary drug under widespread conditions of use after product approval and marketing. PAE sections are based on the established clinical sign frequencies of the

most commonly reported clinical adverse events, as well as safety concerns identified from signal detection and evaluation. Recommendations for the addition of a PAE section are frequently made at the end of the Tier 1 period for a veterinary product. However, they can be made at any time FDA considers the evidence sufficient to warrant the recommended action.

The Tier 1 period lasts for at least the first 24 months after product approval and subsequent marketing. Tier 1 products are transitioned to non-Tier 1 level monitoring after the veterinary safety reviewer and Branch Chief consider the post-approval safety reporting profile of the product relatively stable over time such that a less rigorous level of monitoring is considered appropriate.

B. Non-Tier 1 products

ADEs received for non-Tier 1 products are not routinely reviewed for causality, as the post-approval safety reporting profile for the product is considered established or otherwise warrants less frequent assessment (e.g., products receiving very few cases a year on a consistent basis). Instead, non-Tier 1 products undergo periodic quantitative assessment of their safety reporting profile to determine if important changes over time have occurred. The exception to this is that all cases involving human exposure are reviewed on an on-going basis.

The periodic quantitative assessment is similar to that described for Tier 1 products and includes, but is not limited to, clinical sign frequencies with reporting rates for all approved species, as well as for product defect and medication error cases, human exposure cases, and cases received for unapproved species. The periodic assessment may also include disproportionality analysis depending on the case volume of an individual non-Tier 1 product. Periodic assessments are compared to previous assessments to identify any substantial changes of possible concern in the safety or efficacy of a product. Identified signals from these processes are further assessed by signal evaluation.

If the veterinary safety reviewer concludes, after initial safety signal evaluation, that remedial action is required, the veterinary safety reviewer discusses the conclusion with the veterinary product manager and Branch Chief. At this stage, safety signals may require further evaluation and/or potential remedial actions are identified. Information regarding the safety signal and proposed remedial action(s) is communicated to the ONADE target animal review division. Further discussion between the Offices may occur depending upon the complexity of the signal and proposed remedial actions.

The frequency of a non-Tier 1 product's quantitative assessments depends on the volume of cases received for the product, as well as any on-going concerns that may necessitate more frequent evaluations.

Assignment of non-Tier 1 products to veterinary safety reviewers takes into consideration indicated species, pharmaceutical class, and/or a reviewer's previous experience with a product.

VI. VERSION HISTORY

August 15, 2024 – Original version.