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BY ELECTRONIC SUBMISSION

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Room 1061, HFA-305
Rockville, Maryland 20852

CITIZEN PETITION

Executive Summary

The Pharmaceutical Safety Oversight Council ("Petitioner" or "PSOC")[1], a nonprofit organization dedicated to promoting transparency and accountability in pharmaceutical safety evaluation, respectfully submits this Citizen Petition under 21 C.F.R. § 10.30, in conjunction with Section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b) and 21 C.F.R. Part 514, to request that the U.S. Food and Drug Administration ("FDA"), acting through its Center for Veterinary Medicine ("CVM"), exercise its post-approval oversight authority to impose enforceable safe-use conditions for **Librela (bedinvetmab injection) (NADA 141-562)**, a caninized monoclonal antibody approved for the control of pain associated with osteoarthritis in dogs.

Petitioner acknowledges that Librela addresses a therapeutic need particularly for dogs that cannot tolerate nonsteroidal anti-inflammatory drugs or other conventional analgesics. Petitioner does not seek to eliminate access, but, rather, requests enforceable conditions of use that preserve access for appropriately selected patients while reducing preventable harm in identifiable higher-risk populations. Withdrawal proceedings are requested only in the alternative, should CVM determine that available safe-use conditions are insufficient to ensure that Librela remains safe under its labeled conditions of use.

[1] The Pharmaceutical Safety Oversight Council ("Petitioner" or "PSOC") is a nonprofit organization dedicated to promoting transparency, accountability, and evidence-based standards in pharmaceutical post-market safety evaluation. PSOC conducts independent analysis of post-approval pharmacovigilance data and advocates for enforceable risk communication standards that protect both human and animal patients from preventable drug-related harm. PSOC was founded by Lita Dwight, a graduate of Georgetown University Law Center, whose professional background encompasses corporate and regulatory law and nonprofit governance, and whose work in veterinary pharmaceutical safety advocacy is informed by both her legal training and her direct experience with post-approval adverse events in companion animals. Ms. Dwight serves as Executive Director of PSOC. The independent data analysis supporting this petition was conducted by Jeffrey Gibson, an independent researcher and data analyst specializing in pharmacovigilance signal analysis of publicly available adverse event data.

Several independent lines of evidence — (i) CVM's own Standard Adverse Event Review (DPS-2024-141) ("SAER"), (ii) peer-reviewed studies by board-certified veterinary specialists, and (iii) the known pharmacology of sustained nerve growth factor ("NGF") suppression — collectively establish a serious, persistent, and mechanistically coherent post-market safety signal concentrated in the neurologic and musculoskeletal systems. The signal has continued to accumulate despite CVM's prior communication-based interventions, including labeling revisions, a Dear Veterinarian Letter, and a recommended Client Information Sheet.

As of December 31, 2025, CVM's adverse event database contained **16,042** total adverse drug event ("ADE") reports for Librela, including **2,712** reports in which death or euthanasia was coded as the case outcome.[2] Independent peer-reviewed studies have since documented statistically significant musculoskeletal adverse events consistent with accelerated joint destruction and identified the neurobiological mechanism linking sustained NGF suppression to the neurological adverse event profile in aging dogs.[3]

CVM's own SAER identified positive disproportionality signals across 18 distinct preferred terms; documented an 80% attending veterinarian suspicion rate (compared to 32% for all other drugs); assessed 360 of 363 individual cases as having evidence suggestive of at least a possible causal association; identified 7 positive rechallenge cases; and explicitly rejected the sponsor's hypothesis that the signal reflects social media-driven overreporting. These 363 cases represent a subset of the 766 qualifying cases with signs of concern; due to the large volume of cases, CVM assessed only those reporting at least two signs of concern for the most frequently reported terms.[4]

When considered alongside CVM's own causality assessments, temporal clustering findings, and the published peer-reviewed literature, the substantial and growing safety signal warrants enforceable regulatory action beyond communication-based measures already implemented.

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[2] These figures are pharmacovigilance signal counts derived from spontaneous adverse event reports. While they do not establish incidence, relative risk, or causation, they do reflect a substantial and growing safety signal.

[3] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Freedom of Information, NADA 141-562, Librela (bedinvetmab Injection), (January 22, 2026) (Exhibit 14(c)) [hereinafter "January 2026 FOIA Response"]; Farrell M, et al. Musculoskeletal adverse events in dogs receiving bedinvetmab (Librela). *Front Vet Sci.* (May 9, 2025) (Exhibit 5) [hereinafter "Farrell et al. (Frontiers)"]; Dewey CW, Brunke MW. Commentary: Musculoskeletal adverse events in dogs receiving bedinvetmab (Librela). *Front Vet Sci.* (July 16, 2025) (Exhibit 6) [hereinafter "Dewey & Brunke (Frontiers)"]; Dewey CW, Brunke MW, Dysmetabolism of the Nerve Growth Factor Pathway in the Aging Brain Plays a Pivotal Role in Cognitive Decline, 264 J. AM. VET. MED. ASS'N 471 (2026) (Exhibit 7) [hereinafter "Dewey & Brunke (JAVMA)"]; Von Pfeil DJF, Armitage A, Nelson NC**.** Emerging Signs of Rapidly Progressive Arthritic Changes in Dogs and Cats Receiving Bedinvetmab and Frunevetmab. *Vet Comp Orthop Traumatol.* 2026;39:157–161. doi: 10.1055/a-2846-8347. (Exhibit 19) [hereinafter "Von Pfeil, et. Al. (Vet Comp Ortho)"]

[4] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Standard Adverse Event Review, Librela (bedinvetmab injection), NADA 141-562, DPS-2024-141 (Sept. 10, 2024) (Exhibit 1) [hereinafter "SAER"]

This petition does not seek to relitigate the original approval decision. It instead addresses whether the evolving post-market record now demonstrates the need for stronger, enforceable conditions of use to ensure that Librela continues to satisfy the statutory requirement that an approved new animal drug remain safe under its labeled conditions of use. *See* 21 U.S.C. § 360b(a), (d), and (e).

Each of these requested actions has a direct precedent in CVM's own prior regulatory practice — specifically, the comprehensive Risk Minimization Action Plan that CVM implemented for ProHeart 6 (moxidectin) following voluntary withdrawal in 2004 and that remains in effect today for both ProHeart 6 and ProHeart 12.

Accordingly, Petitioner respectfully requests that CVM take the following actions:

A. Post-Approval Safety Studies. Require sponsor-conducted, CVM-supervised post-approval studies designed to evaluate neurologic and musculoskeletal safety outcomes in representative real-world populations, with predefined endpoints, independent Data Safety Monitoring Board (DSMB) oversight, adequate follow-up, and transparent reporting.

B. Prominent Labeling Revisions. Require prominent labeling revisions commensurate with the seriousness of the reported outcomes, including a prominently displayed boxed or equivalently conspicuous warning addressing serious neurologic adverse events, reported death outcomes, the potential for accelerated joint destruction, the absence of long-term safety data beyond nine months, and the prolonged, non-readily reversible effects of sustained NGF suppression.

C. Prescribing Prerequisites. Require enforceable prescribing prerequisites, including documented radiographic confirmation of osteoarthritis before treatment initiation, baseline neurologic assessment, and defined screening criteria for dogs at elevated risk, and documented reassessment before each subsequent dose.

D. Standardized Owner-Facing Risk Disclosure and Enhanced Pharmacovigilance. Require standardized owner-facing risk disclosure before first administration, documented acknowledgment of receipt, enhanced adverse event reporting frequency, quarterly distribution data sufficient to support denominator-based analysis, and development of a denominator-based real-world surveillance system.

E. Updated CVM Safety Communication and Public Resource. Issue an updated Dear Veterinarian communication and maintain a dedicated CVM public resource that consolidates current safety information, discontinuation guidance, and reporting expectations.

F. Independent Advisory Committee Review. Convene an ad hoc advisory committee under 21 C.F.R. Part 14 to conduct an independent public review of Librela's post-market safety record, consistent with the advisory review CVM previously conducted through the Veterinary Medicine Advisory Committee ("VMAC") in connection with the ProHeart 6/12 RiskMAP.[5]

G. Alternative Request. If CVM determines that the measures described above are infeasible or insufficient to provide reasonable assurance of safe use, initiate appropriate proceedings under 21 U.S.C. § 360b(e).

H. Request for Meeting. Grant Petitioner an opportunity to meet with CVM staff pursuant to 21 C.F.R. § 10.65(c) to discuss the safety concerns raised in this petition and the requested actions.

These requested actions fall within CVM's existing statutory and regulatory authority[6] and are consistent with the risk-mitigation framework CVM previously implemented for ProHeart 6 (moxidectin) under demonstrably less severe post-market safety circumstances.

In light of the continued accumulation of serious post-market reports despite prior communication-based measures, Petitioner respectfully submits that enforceable safeguards are now necessary to ensure that Librela remains safe under its labeled conditions of use while preserving access for appropriately selected patients.

I. Action Requested

Pursuant to 21 C.F.R. § 10.30(b)(3), Petitioner requests that the Commissioner, acting through the CVM, take the following actions with respect to Librela (bedinvetmab injection) (NADA 141-562). The factual and legal grounds supporting each requested action are set forth in Section II.A (Factual Background) and Section II.B (Legal

[5] The Veterinary Medicine Advisory Committee (VMAC) — originally chartered at 49 Fed. Reg. 28,093 (July 9, 1984) and most recently convened for ProHeart 6 in 2005 and 2010 — was the advisory body established specifically to advise CVM on animal drug safety and efficacy. Although VMAC's charter was terminated in 2013, see 78 Fed. Reg. 69,991 (Nov. 22, 2013), the Commissioner retains full authority under 21 C.F.R. § 14.40(a) to recharter VMAC or establish an ad hoc advisory committee "whenever it is necessary or appropriate" to review a matter before FDA. Nothing in the FDC Act or CVM's regulations limits this authority to cases involving products that have already been voluntarily withdrawn.

[6] 21 U.S.C. §§ 352(a), 352(f), 360b(a), 360b(b)(1)(H), 360b(d), and 360b(e); 21 C.F.R. §§ 10.30, 201.105, 514.80(b)(4), 514.80(b)(5)(i), and Part 514

Background) below. The argument demonstrating why each action is warranted is set forth in Section II.C (Argument) below.

A. Post-Approval Safety Studies with Independent Oversight

Petitioner requests that CVM require sponsor-conducted, CVM-supervised post-approval studies designed to characterize neurologic and musculoskeletal safety outcomes under real-world conditions of use and to identify patient-level risk factors for serious adverse events. Such studies should address the following objectives:

(i) Prospective Design with Defined Denominators

- A prospective, multi-center study design (pragmatic trial or prospective cohort) with a clearly defined denominator of exposed dogs and prespecified outcome definitions.
- Inclusion of an active-comparator or concurrent-control cohort where feasible, to contextualize background event rates in the indicated population.

(ii) Musculoskeletal Structural Monitoring

- Baseline and longitudinal imaging of index and non-index joints using standardized positioning and interpretation criteria.
- Imaging at baseline, and at clinically appropriate intervals (e.g. 6, 12, and 24 months or until discontinuation), with predefined triggers for unscheduled imaging upon new or worsening lameness or sudden functional decline, or suspected accelerated joint pathology.
- Prespecified structural endpoints, including joint space narrowing, subchondral bone change, osteophyte progression, pathological fracture, joint luxation, and other objective markers of accelerated joint pathology or destruction.
- Independent, blinded radiographic review by qualified specialists without financial relationships with the sponsor.

(iii) Neurologic Outcomes Assessment

- Baseline and serial neurologic evaluations using standardized assessment elements (gait analysis, proprioception testing, postural reactions, cranial nerve assessment) at each dosing visit and at prespecified follow-up intervals.
- Prespecified definitions and severity grading for neurologic events including ataxia, paresis, paralysis, seizures, collapse, and recumbency.
- Independent clinical adjudication for serious neurologic events and death outcomes.
- Positive rechallenge and dechallenge documentation for any neurologic event, including complete narrative, timing, and outcome data.

(iv) Representative Population and Subgroup Analyses

- Enrollment reflective of intended use: older dogs with confirmed osteoarthritis, including common comorbidities and typical concomitant medications.
- Prespecified subgroup analyses by age, breed, renal and hepatic function, prior neurologic history, and concurrent analgesic use, to identify higher-risk profiles.

(v) Duration, Follow-Up, and Discontinuation Capture

- Minimum observation period of 12 months, with extended follow-up for dogs maintained on therapy beyond that period.
- Systematic capture of all discontinuations and reasons, dose timing, and re-dosing decisions.

(vi) Independent Oversight and Reporting

- An independent Data Safety Monitoring Board ("DSMB") with prespecified interim stopping rules and authority to recommend study modification or suspension.
- DSMB composition to include relevant veterinary specialty expertise and independent biostatistical expertise, with no member having a financial relationship with the sponsor.
- Periodic interim analyses submitted to CVM, with public-facing summaries suitable for veterinarians and pet owners.
- Protocol submission to CVM for review and concurrence prior to initiation, with periodic and final reports on a CVM-specified timeline.[7]

B. Prominent Labeling Revisions

Petitioner requests that CVM require revisions to the Librela prescribing information to reflect the seriousness of the post-approval safety record and to operationalize enforceable safe-use

[7] Petitioner notes that a 56-day sponsor-funded comparative study recently published in the peer-reviewed literature (Innes et al., 2025) does not satisfy the need for the studies requested herein. That study excluded dogs with pre-existing neurological conditions — precisely the population most relevant to the neurological safety signal — used a duration insufficient to detect structural joint pathology (including RPOA-consistent musculoskeletal pathology documented by Farrell et al., which manifested at a mean of 12.7 injections (approximately 12–13 months) after treatment initiation), and addressed a comparative efficacy question rather than the longitudinal safety characterization that CVM's own SAER identified as the critical unmet need. The research investment required to answer the questions raised by the post-approval record has not been made voluntarily and cannot reasonably be expected absent a formal FDA mandate.

conditions. Petitioner seeks a prominently displayed boxed or equivalently conspicuous warning, together with the additional labeling elements set forth below.

(i) Prominently Displayed Boxed or Equivalent Warning

Petitioner requests that CVM require addition of a prominently displayed boxed or equivalently conspicuous warning containing substantially the following:

> **WARNING: SERIOUS NEUROLOGICAL ADVERSE EVENTS, RISK OF DEATH, AND POTENTIAL FOR ACCELERATED JOINT DESTRUCTION**
>
> Post-approval adverse event reports have identified serious neurological adverse events in dogs treated with LIBRELA, including ataxia, paresis, paralysis, seizures, proprioceptive deficits, recumbency, and collapse. Death (including euthanasia) has been reported as an outcome.
>
> These events were not characterized in pre-approval studies.
>
> In human clinical trials of anti-NGF monoclonal antibodies, rapidly progressive osteoarthritis (RPOA) — accelerated structural joint destruction — was identified as a drug-related adverse event. No systematic radiographic evaluation for RPOA was conducted in LIBRELA pre-approval studies. Post-approval peer-reviewed analysis has identified musculoskeletal adverse events consistent with accelerated joint pathology in dogs receiving bedinvetmab.
>
> **Long-term safety data beyond 9 months are not available. NGF suppression is not readily reversible following LIBRELA administration. Veterinarians must counsel pet owners regarding these risks prior to initiating therapy, conduct neurologic assessments at each dosing visit, and immediately discontinue treatment upon any discontinuation trigger set forth in the Warnings and Precautions section.**

Whether CVM grants the request for prominently displayed boxed or equivalent warning, Petitioner further requests the following additional labeling elements:

(ii) Explicit Contraindications and Exclusions

- Clearly defined contraindications for dogs at elevated risk based on the post-approval record and mechanistic plausibility, including dogs with pre-existing neurologic disease, active seizure disorder, or documented cognitive dysfunction.

(iii) Enumerated Clinical Stop Rules and Mandatory Discontinuation Criteria

Petitioner requests that the prescribing information include explicit, clinical stop rules requiring veterinarians to immediately discontinue bedinvetmab, withhold any scheduled dose, and conduct a clinical evaluation upon observation of any of the following:

- **Neurologic discontinuation triggers:**
    - New-onset ataxia, gait instability, or incoordination not attributable to musculoskeletal pain alone
    - Paresis or paralysis of any limb
    - Seizure activity of any type, including first-onset seizures
    - Acute or progressive recumbency with inability to rise
    - Vestibular signs of acute onset (head tilt, nystagmus, falling)
    - Collapse or sudden loss of consciousness
    - Proprioceptive deficits (knuckling, delayed postural reactions) not previously documented
- **Musculoskeletal discontinuation triggers:**
    - Acute non-weight-bearing lameness of sudden onset not attributable to known injury
    - Rapid deterioration of a previously stable joint, particularly non-index joints
    - Clinical or radiographic findings consistent with accelerated joint destruction (RPOA), pathological fracture, or joint luxation[8]
    - Marked worsening of lameness despite continued dosing
- **Systemic discontinuation triggers:**
    - Acute renal deterioration within 30 days of dosing, particularly in dogs with concurrent or recent NSAID use
    - Rapid unexplained weight loss, severe anorexia, or significant decline in body condition score

[8] Rapidly Progressive Osteoarthritis (RPOA): a form of accelerated joint destruction — was characterized in humans treated with anti-NGF monoclonal antibodies in clinical trials. Post-approval peer-reviewed analysis (Farrell et al., (Frontiers) (Exhibit 5)) documented musculoskeletal adverse events in dogs treated with bedinvetmab — including accelerated joint destruction, pathological fractures, and joint luxations — that an independent panel of 18 board-certified veterinary specialists assessed as having a strong causal association with bedinvetmab. The long-term structural effects of bedinvetmab on canine joint architecture have not been systematically characterized in controlled post-approval studies.

- **Re-dosing prohibition:**
    - Bedinvetmab shall not be re-administered to any dog that has experienced a mandatory discontinuation trigger without documented resolution, a documented alternative causal explanation, and a documented discussion with the owner of the risks of re-administration in light of positive-rechallenge pharmacovigilance findings.

(iv) Enhanced Concomitant Therapy Guidance

- Clear precautions regarding concomitant NSAID and other analgesic use, including monitoring expectations and conservative decision points.

(v) Restructured Adverse Reactions Section

- Prominent listing and grouping of neurologic and musculoskeletal adverse events reported post-approval, with severity framing that includes serious outcomes and death outcomes, and guidance for clinical recognition, response, and reporting.

C. Prescribing Prerequisites

Petitioner requests that CVM require enforceable prescribing prerequisites that align treatment initiation with confirmed indication, establish an objective baseline for monitoring, and condition continued dosing on documented reassessment.

(i) Documented Confirmation of Osteoarthritis Prior to Initiation

- Require documented confirmation of osteoarthritis prior to first dosing, including radiographic or other objective diagnostic confirmation appropriate to the affected joint(s), with records retained in the medical file. This requirement serves both diagnostic appropriateness and the establishment of a structural baseline for subsequent monitoring for accelerated joint pathology.

(ii) Baseline Assessment and Risk Screening

- Require documentation of baseline neurologic screening and relevant medical history, including prior neurologic events, collapse episodes, or unexplained weakness.
- Require baseline cognitive function assessment, particularly in dogs aged 8 years or older.
- Require baseline evaluation of major comorbidities relevant to safe use, with clear defined triggers for additional workup or exclusion from treatment.

(iii) Longitudinal Monitoring and Radiographic Follow-up

- Require that continued dosing be contingent on documented reassessment at each dosing interval, including neurologic status and mobility evaluation.
- Require that reassessment findings be documented, retained in the patient's medical record, and linked to any adverse event reports submitted to CVM.
- Require follow-up imaging at clinically appropriate intervals (e.g. every 6-12 months) for dogs maintained on long-term therapy and for any dog presenting with new lameness, reduced response or suspected structural deterioration.

D. Standardized Owner-Facing Risk Disclosure and Enhanced Pharmacovigilance

Petitioner requests enforceable, standardized risk communication and pharmacovigilance controls:

(i) CVM-Reviewed Client Information Sheet

- Require an updated, standardized, CVM-reviewed Client Information Sheet that must be provided to and reviewed with the pet owner before first dosing and before each subsequent dose, summarizing serious reported risks, including death outcomes, key warning signs requiring immediate veterinary contact, and instructions for when to seek urgent care and discontinue further dosing. The Client Information Sheet should serve, as it does under the ProHeart 6/12 RiskMAP, as a tool for the veterinarian to facilitate an informed discussion with the client prior to each administration.

(ii) Documented Acknowledgment of Receipt

- Require written acknowledgment signed and dated by the pet owner and retained in the medical record — confirming that the Client Information Sheet was provided and reviewed, and that risk counseling, including stop rules and reporting instructions, was conducted.

(iii) Prescriber Education

- Require that the sponsor develop, maintain, and distribute a CVM-reviewed prescriber education resource addressing patient selection, contraindications, monitoring requirements, stop rules, and adverse event reporting expectations. This element is modeled on the web-based training and certification program required under the ProHeart 6/12 RiskMAP.

(iv) Enhanced Adverse Event Reporting

- Under 21 C.F.R. § 514.80(b)(5)(i), require that the sponsor submit ADE reports at enhanced frequency, including weekly reporting for fatal outcomes and serious neurological adverse events, and quarterly comprehensive ADE data submissions with standardized fields to improve completeness and interpretability.

- Require a sponsor-administered registry (CVM-specified and CVM-auditable) capturing standardized exposure and outcome data — including concomitant medications, diagnostic findings, discontinuations, and mortality — with periodic summary submissions to CVM.

(v) Quarterly Distribution Data

- Require quarterly submission of product distribution data under 21 C.F.R. § 514.80(b)(4), including total units distributed, to permit construction of a meaningful exposure denominator for pharmacoepidemiological analysis. Request that distribution data be made publicly available in anonymized aggregate form.

(vi) Denominator-Based Surveillance Infrastructure

- Request that CVM engage with veterinary practice networks to establish a denominator-based real-world evidence surveillance system using electronic health record data, to provide the incidence data that the spontaneous reporting system structurally cannot generate.

(vii) International Regulatory Coordination

- Request that CVM formally inquire with the European Medicines Agency (EMA), the UK Veterinary Medicines Directorate (VMD) and Health Canada regarding any post-approval safety actions taken for bedinvetmab, and that such information be incorporated into the administrative record for this petition.

E. Updated CVM Safety Communication and Public Resource

- Request that CVM issue an updated Dear Veterinarian communication contemporaneous with any labeling revision, reflecting enforceable safe-use conditions including prescribing prerequisites, stop rules, owner disclosure requirements, enhanced reporting expectations, and monitoring guidance.

- Request that CVM establish and maintain a dedicated, publicly accessible web resource for Librela consolidating current safety information, discontinuation guidance, and reporting expectations, updated on a rolling basis.
- Request dissemination through CVM's veterinary practitioner communication networks, veterinary professional organizations, and state veterinary medical boards.

F. Convening of an Independent Advisory Committee Review

- Request that CVM convene an Independent Advisory Committee Review to publicly review the post-market safety record for Librela (bedinvetmab injection), consistent with CVM's prior convening of VMAC in connection with ProHeart 6 on January 31, 2005 and March 24, 2010.

G. Alternative Request

Should CVM determine that the measures described in Requested Actions A through F are infeasible or insufficient to provide reasonable assurance that bedinvetmab can be used safely under its labeled conditions of use, Petitioner requests that CVM initiate appropriate proceedings under 21 U.S.C. § 360b(e). This alternative is included to preserve the full scope of CVM's statutory authority should the primary requested actions prove insufficient or infeasible.

H. Request for Meeting

Pursuant to 21 C.F.R. § 10.65(c), Petitioner requests an opportunity to meet with CVM staff to discuss the safety concerns raised in this petition, the scientific questions raised by the post-approval data, and the practical implementation of the requested enforceable safe-use conditions. Petitioner further notes that the post-market adverse events documented herein have affected numerous families who have experienced significant loss — emotional, financial, and personal — following the serious injury or death of their companion animals. A meeting would afford CVM the opportunity to hear directly how these losses have affected the families behind the adverse event reports, in a manner that the written record alone cannot fully convey.

II. Statement of Grounds

A. Factual Background

The following factual record is presented in support of the requested actions. It draws upon several sources, including: (i) FDA's own published pharmacovigilance analyses, (ii) the Freedom of Information Summary for NADA 141-562, (iii) the approved and revised Librela prescribing information, (iv) published peer-reviewed literature, (v) Congressional testimony, (vi) CVM Precedent ProHeart 6/12 RiskMAP Meeting [transcript], (vii) FOIA-obtained adverse

event data and (viii) publicly available regulatory records from domestic and international jurisdictions.

(i) Librela: Product Description, Mechanism of Action, and Pharmacokinetic Profile

Librela (bedinvetmab injection) is a caninized recombinant monoclonal antibody approved under NADA 141-562 for the control of pain associated with osteoarthritis in dogs.[9] It was approved on May 5, 2023, and first marketed on July 14, 2023.[10] The product is manufactured and distributed by Zoetis Inc. (Kalamazoo, Michigan).[11]

Bedinvetmab binds to and inhibits the biological activity of canine nerve growth factor ("NGF"), which has been found to be elevated in dogs with osteoarthritis.[12] It is administered by subcutaneous injection once monthly, dosed by weight range to target a minimum dose of 0.5 mg/kg.[13] The product is available as a sterile buffered solution in 5, 10, 15, 20, and 30 mg/mL concentrations in single-use vials.[14]

The approved labeling reports a mean elimination half-life of approximately 15.8 days following a single dose and approximately 19.0 days at steady state under field conditions.[15] Monthly dosing results in drug accumulation, with steady-state concentrations achieved after approximately two doses.[16]

Once administered, sustained NGF suppression continues for weeks: a characteristic that distinguishes bedinvetmab from conventional analgesics. There is no pharmacological reversal agent for bedinvetmab.[17] A veterinarian who observes an adverse event following administration cannot reverse the drug's activity; systemic clearance may take weeks or months, depending on the number of prior doses and the degree of drug accumulation.

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[9] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Freedom of Information Summary, NADA 141-562, Librela (bedinvetmab Injection), at 1 (May 5, 2023) (Exhibit 8) [hereinafter "Librela FOI Summary"].
[10] SAER at 3
[11] Librela FOI Summary at 5
[12] *Id*. at 2
[13] *Id*. at 2
[14] *Id*. at 5
[15] Original Librela Prescribing Information, Pharmacokinetics section (Exhibit 9(a)) [hereinafter "Original Librela PI"]; *see also* Revised Librela Prescribing Information, Pharmacokinetics section (Exhibit 9(b)) [hereinafter "Revised Librela PI"]
[16]Original Librela PI, Pharmacokinetics section.
[17]There is no approved reversal agent for bedinvetmab. The approved labeling does not reference any pharmacological antagonist.

(ii) The Biological Functions of Nerve Growth Factor Beyond Nociception

NGF is not solely a pain mediator. It is a pleiotropic neurotrophic protein with critical roles across multiple physiological systems. The approved Librela prescribing information itself acknowledges several of these functions:

- NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals.[18]
- Long-term effects beyond nine months of Librela use have not been evaluated.[19]
- NGF is expressed within the heart and vasculature, and the long-term effects of reduced NGF in dogs with cardiac disease are unknown.[20]
- Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies, including reduced size and number of neurons.[21]

Beyond these label disclosures, the published scientific literature establishes that NGF plays critical roles in:

- ***Neuronal survival and maintenance*:** NGF is essential for the survival and function of cholinergic neurons in the basal forebrain — the same neuronal population whose degeneration is a defining feature of Alzheimer's disease in humans and canine cognitive dysfunction syndrome ("CCDS") in dogs — and their vulnerability increases with age. [22] Published research in transgenic mouse models demonstrates that even peripherally produced anti-NGF antibodies can disrupt the blood-brain barrier through sympathetic nervous system damage, subsequently entering the brain and producing an Alzheimer's-like neurodegenerative scenario without requiring direct CNS penetration.[23] This finding is directly relevant to bedinvetmab: sustained peripheral NGF blockade in vulnerable geriatric dogs may compromise the blood-brain barrier through the same mechanism, potentially enabling central neurodegeneration in the very population for whom the drug is indicated.[24]
- ***Immune regulation*:** NGF is produced by multiple immune cell types, including mast cells, macrophages, and lymphocytes. Immune cells express NGF receptors (TrkA and

[18]Original Librela PI, Precautions section
[19]*Id.*
[20]*Id*; SAER at 3–4.
[21]Original Librela PI, Precautions section
[22]Dewey CW, Brunke MW. Dysmetabolism of the nerve growth factor pathway in the aging brain. *J Am Vet Med Assoc.* (Dec. 2025) at 474 (Exhibit 7) [hereinafter "Dewey & Brunke (JAVMA)"]
[23]Capsoni S, Tiveron C, Amato G, Vignone D, Cattaneo A, Peripheral neutralization of nerve growth factor induces immunosympathectomy and central neurodegeneration in transgenic mice, J Alzheimers Dis 2010;20(2):527–546; discussed in Dewey & Brunke (JAVMA) at 473
[24]Dewey & Brunke (JAVMA) at 473-474

p75NTR), and NGF participates in neuro-immune communication, influencing immune cell survival, activation, and cytokine release.[25]

- ***Peripheral and autonomic nervous system function*:** NGF supports the maintenance and repair of peripheral and sympathetic nerve fibers.[26] The label's acknowledgment regarding primate postganglionic neuronal changes reflects the known dependence of these systems on ongoing NGF signaling.[27]
- ***Musculoskeletal joint repair, bone homeostasis, and structural integrity*:** NGF plays an indispensable regulatory role in the development, homeostasis maintenance, and pathological processes of the skeletal system. Through its receptors TrkA and p75NTR, NGF is involved in bone formation, bone resorption, pain perception, and injury repair.

  Specifically:
  - The NGF receptor (NGFR/p75NTR) is upregulated in skeletal cells during osteoarthritis and plays an essential role in the remodeling and repair of osteoarthritic joints; NGFR deficiency impairs bone formation and enhances bone resorption, resulting in reduction of subchondral bone.
  - Inhibition of NGF-TrkA signaling not only attenuates innervation, vascularization, and ossification in developing endochondral bone, but also impairs fracture repair.
  - NGF-TrkA signaling is acutely upregulated following stress fracture and is required for triggering reinnervation, vascularization, and osteoblastic activity during repair.

The pharmacological suppression of NGF via a long-half-life monoclonal antibody in geriatric dogs — animals already experiencing degenerative joint disease in which NGF-NGFR signaling may be actively compensating for ongoing structural damage — carries biologically plausible risk of interfering with the skeletal repair and remodeling processes most active in the osteoarthritic joint being treated. The breadth of NGF's biological functions establishes the mechanistic plausibility of a multisystem adverse event profile following sustained pharmacological suppression. The post-approval adverse event record is concentrated in these biological domains.[28]

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[25]See, e.g., Aloe L, et al. Nerve growth factor: from the early discoveries to the potential clinical use. *J Transl Med*. 2012;10:239

[26]Dewey & Brunke (JAVMA) at 473

[27]Original Librela PI, Precautions section

[28]*See* Luo Y, et al. NGFR/p75NTR mediates osteoarthritic subchondral bone remodeling. *Nat Commun.* 2024;15:3108 (documenting NGFR/p75NTR role in osteoarthritic joint remodeling and repair); Seidel MF, Netzer C, Chobaz V, Hügle T, Geurts J. Localization of Nerve Growth Factor Expression to Structurally Damaged Cartilaginous Tissues in Human Lumbar Facet Joint Osteoarthritis. *Front Immunol.* 2022;13:783076 (March 2022)

(iii) Pre-Approval Development Program: Studies, Design Boundaries, and Basis for Approval

FDA determined that Librela is safe and effective when used according to the labeling, based on the data submitted by the sponsor.[29]

The pre-approval evidentiary record consisted of the following principal studies:

(a) Effectiveness Studies

Two field studies — one conducted in the United States and one in the European Union — evaluated the effectiveness of Librela for the control of pain associated with osteoarthritis in dogs. Both studies enrolled client-owned dogs diagnosed with osteoarthritis based on physical examination, orthopedic examination, and radiography. Dogs received either Librela or sterile saline by subcutaneous injection every 28 days for a total of three doses. [30]

Effectiveness was measured using the Canine Brief Pain Inventory ("CBPI"), an owner-reported assessment tool. A dog was considered a treatment success if there was a reduction of ≥ 1 in the pain severity score and ≥ 2 in the pain interference score on Day 28 compared to baseline.[31]

The U.S. field study did not demonstrate a statistically significant difference in treatment success rates between the treatment and control groups on its primary effectiveness endpoint at Day 28.[32] While the U.S. and EU studies had similar success rates in the treatment groups (48% and 45.2%, respectively), there was large variability in the control group success rates (36.1% in the U.S. versus 17.0% in the EU), resulting in a larger treatment effect in the EU study.[33]

FDA concluded that, taken together, the weight of evidence from the two field studies demonstrated that Librela is effective at controlling pain associated with osteoarthritis in dogs when at least two doses are given 28 days apart.[34]

(discussing NGF as pivotal mediator in bone remodeling); Reyes MR, et al. NGF-TrkA signaling is required for fracture repair. *Sci Rep.* 2020;10:22241 (establishing NGF-TrkA signaling as required for fracture repair and vascularization); Chen K, Chen L, Ma Y, Chen S, Liu J, Zhou H, Chen Y, Liu G. From neuromodulation to bone homeostasis: therapeutic targets of nerve growth factor in skeletal diseases. *Front. Pharmacol.* 2025;16:1614542. doi:10.3389/fphar.2025.1614542 (describing NGF role in skeletal homeostasis, fracture healing, and osteoporosis pathophysiology).

[29] Librela FOI Summary at 6

[30] *Id*.

[31] *Id*.

[32] *Id*.

[33] *Id*.

[34] *Id*. at 7

(b) Target Animal Safety Studies

The principal safety study was a 6-month laboratory safety study conducted in young, healthy, intact Beagles administered Librela by subcutaneous injection every 28 days for a total of 7 doses at 0X, 1X (1 mg/kg), 3X (3 mg/kg), or 10X (10 mg/kg) the high end of the inherent dose band.[35] Dogs in the 3X and 10X treatment groups had scabbing lesions of the head and neck. Boney changes, including boney remodeling and cartilage degeneration, were seen in one dog in the 3X treatment group; the FOI summary states that "the dog may have had an underlying musculoskeletal condition that caused the boney changes; however, a relationship to treatment cannot be ruled out".[36] Additionally, one dog in the 1X (1 mg/kg) treatment group — the approved dose range — showed early cartilage breakdown in both forelimbs: focal proteoglycan depletion with mild cartilage necrosis in the left ulna, and erosion and degeneration of the cartilage in the right ulna.[37]

A 2-week laboratory study evaluated concurrent administration of one Librela injection and 14 days of an injectable NSAID. The FOI summary states: "Although there were no significant findings, this limited laboratory study did not provide sufficient data to support the safety of concurrent use of Librela and NSAIDs."[38]

An additional 3-month exploratory laboratory safety study used a non-final formulation of bedinvetmab. Both gross and microscopic skin lesions were observed at the injection site in all treatment groups.[39]

Some dogs from the EU field study were enrolled in a 6-month continuation phase to evaluate the safety of 6 additional monthly doses; there was no control group in this phase.[40] During this continuation, two dogs presented with rear limb paresis of unknown etiology. One dog responded to ongoing NSAID treatment; the other did not respond and was euthanized.[41]

(c) Study Duration and Dosing

Both the U.S. and EU field studies were limited to an 84-day observation period with a maximum of three monthly doses.[42] The continuation phase of the EU field study extended dosing to 9 months.[43] Librela is indicated and used for ongoing monthly administration in a

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[35] *Id*. at 18-19
[36] *Id*. at 21(Target Animal Safety section)
[37] *Id.* at 21-22 (Target Animal Safety section)
[38] Librela FOI Summary at 22
[39] *Id*.
[40] *Id*. at 2
[41] *Id*. at 17, Continuation Phase section.
[42] *Id*. at 10; SAER at 4
[43] Librela FOI Summary at 7 and 17

chronic condition, frequently for periods far exceeding 9 months. The labeling itself acknowledges: "Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated".[44]

(d) Study Population

While the field studies enrolled dogs ranging from 1 to 17.5 years old, neither the field studies nor the target animal safety study was designed or powered to evaluate safety specifically in the geriatric subpopulation that constitutes the overwhelming majority of dogs treated post-approval. CVM's SAER documented that 72.9% of post-approval adverse event cases were reported in dogs aged 10 years or older; by comparison, only 17.7% of cases for all other drugs in CVM's database occurred in this age group. CVM noted that the average age of osteoarthritis diagnosis in dogs is 8–13 years and that it is "not unusual to see that most dogs using this product fell within the 6yr – > 10yr old age range.".[45]

(e) Monitoring Parameters

The field studies used owner-reported CBPI scores as the primary outcome measure. Neither the field studies nor the target animal safety study incorporated:

- Systematic radiographic monitoring with prespecified structural endpoints for joint pathology;[46]
- Standardized, objective neurologic assessments (gait analysis, proprioception testing, postural reactions);[47]
- Prespecified endpoints for neuromuscular adverse events.[48]

(f) Adverse Events Reported in Pre-Approval Studies

The most common adverse reactions reported in the U.S. field study were: urinary tract infection (11.1%), bacterial skin infection (8.1%), dermatitis (7.4%), dermal mass (5.9%), erythema (4.4%), dermal cysts (3.0%), pain on injection (3.0%), inappropriate urination (3.0%), and histiocytoma (2.2%).[49] No neurologic adverse events of any kind were reported.

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[44]Original Librela PI at Precaution section; SAER, at 4.
[45] SAER, at 20 and Table 2.1.2 (age distribution of Librela cases)
[46] Librela FOI summary at 7-8 (describing study designs; no systematic radiographic monitoring protocol described).
[47]*Id*. at 7-8 (no standardized neurologic assessment protocol described).
[48]*Id*. (no prespecified endpoints for neuromuscular adverse events).
[49]Original Librela PI, Adverse Reactions section; SAER at 4, Table 2. (Number (%) of Dogs with Adverse Reactions Reported in the U.S. Field Study)

The most common adverse reactions in the EU field study were: increased blood urea nitrogen (13.8%), lethargy (3.6%), emesis (2.9%), anorexia (2.2%), lameness (2.2%), and cough (2.2%).[50] Two dogs in the EU study were euthanized: a 13-year-old Bichon Frise with pre-existing renal and cardiac disease, and an 8-year-old mixed breed with pancreatitis.[51]

During the EU continuation phase, one dog enrolled for stifle osteoarthritis developed acute forelimb lameness diagnosed as elbow dysplasia, and two dogs presented with rear limb paresis of unknown etiology.[52]

Additionally, one dog started on NSAIDs on Day 7 for osteoarthritis-associated pain had NSAIDs discontinued on Day 10 due to anorexia and gastroenteritis, with azotemia worsening at Day 13; the dog received no further Librela treatment.[53]

(g) Concurrent NSAID Use

The 2-week concurrent-use study did not provide sufficient data to support the safety of concurrent Librela and NSAID use. The current prescribing information states: "The safe use of anti-NGF monoclonal antibodies with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in dogs".[54]

(iv) International Labeling Discrepancies

Librela received European marketing authorization in November 2020 and was commercially launched in the EU in February 2021. Health Canada approved Librela on March 8, 2023 — approximately two months before U.S. approval — with a package insert label dated October 2022 reflecting post-market experience accumulated since the earlier European commercial launch in February 2021.[55]

The evolution of Canadian labeling across three documented versions establishes a pattern directly relevant to the adequacy of the U.S. label at launch. Petitioner respectfully requests that CVM formally examine whether Zoetis's pharmacovigilance obligations under 21 C.F.R. §

[50]Original Librela PI, Adverse Reactions section; SAER at 5, Table 3. (Number (%) of Dogs with Adverse Reactions Reported in the European Field Study)
[51]SAER at 5
[52]*Id.*
[53]*Id.*
[54] Original Librela PI, Precautions section; SAER at 3
[55] Zoetis Canada Inc., LIBRELA (bedinvetmab injection) Canadian Package Insert, DIN 02511797 et al. (October 17, 2022) (Exhibit 10(b)) [hereinafter "Canadian Package Insert 2022"]; European Medicines Agency, CVMP Assessment Report for Librela (bedinvetmab), EMA/518235/2020 (Jan. 5, 2021) (Exhibit 10(a)) [hereinafter "EMA CVMP Assessment Report"];

514.80(a)(1)–(2) — which expressly require reporting of foreign-source safety data — were satisfied with respect to the Canadian label disclosures.

January 2021 — Canadian Regulatory Submission. The Canadian regulatory submission package insert prepared by Zoetis in January 2021 contained an adverse reactions section identical in substance to what would become the U.S. label at launch in May 2023: confined to dermatological, gastrointestinal, urinary tract, and injection-site events. No ataxia. No seizures. No death. No neurological signs of any kind. However, this same January 2021 document disclosed, in its Adverse Reactions narrative, that during the EU 6-month open-label continuation study, two dogs developed mild or moderate proprioceptive deficits that were "not considered to be related to osteoarthritis" and for which "the causality for these events was not determined." It further disclosed, in the Animal Safety section, that one dog in the concurrent-use safety study developed "minimal perivascular mononuclear cell infiltrates and gliosis of the spinal cord" following Librela administration.[56]

October 2022 — Canadian Approved Package Insert. By October 17, 2022 — seven months before the U.S. label was approved and nine months before U.S. commercial launch — Zoetis had updated the Canadian package insert for Librela to reflect post-market experience accumulated since the earlier European and Canadian commercial launches. The October 2022 Canadian label, bearing the actual Drug Identification Numbers assigned by Health Canada (DIN 02511797), listed the following as known post-approval adverse events in the "rare" frequency category (defined as at least 1 but not more than 10 animals in 10,000 animals treated)[57]:

> ***Systemic disorders****: lack of efficacy, polydipsia,* ***death****, lethargy, anorexia.*
> ***Renal and urinary tract disorders****: polyuria, urinary incontinence.*
> ***Digestive tract disorders****: diarrhea, vomiting.*
> ***Neurological disorders****:* ***ataxia, seizure****.*

The Canadian label further disclosed that hypersensitivity reactions and immune-mediated diseases had been reported very rarely. The section heading explicitly identifies these as post-approval findings based on voluntary adverse event reporting from commercial use.

The U.S. label approved in May 2023 listed none of these events. The adverse reactions section of the U.S. label at commercial launch in July 2023 — published nine months after the October 2022 Canadian update — contained only: urinary tract infection, bacterial skin infection,

[56] Zoetis Inc., Draft Product Labels, LIBRELA (bedinvetmab injection), Canadian Regulatory Submission Package Insert Mock-Up, Zoetis Version — January 28, 2021 (Exhibit 10(d)) [hereinafter "Canadian Product Label Mock-up 2021"], Adverse Reactions section (proprioceptive deficits, undetermined causality) and Animal Safety section (gliosis of the spinal cord).

[57] Canadian Package Insert 2022, Adverse Reactions section at 3 (listing death, ataxia, and seizure as post-approval adverse events in the "rare" frequency category based on post-market experience).

dermatitis, dermal mass, erythema, dermal cysts, pain on injection, inappropriate urination, and histiocytoma. No ataxia. No seizures. No death. No neurological signs of any kind. No polydipsia. No polyuria. These events did not appear in the U.S. labeling until the January 2025 revision, eighteen months after commercial launch and following CVM's issuance of the Dear Veterinarian letter in December 2024.[58]

June 2024 — Further Update. The Canadian product monograph was again updated in June 2024, continuing to reflect the evolving post-market safety record.[59]

The significance of this chronology is precise. At the time Zoetis submitted its U.S. NADA application for CVM review — and at the time CVM approved it in May 2023 — an approved, marketed Canadian label for the identical product, administered to the same species via the same route, already listed death and ataxia as known post-approval adverse reactions. These were not theoretical risks or foreign-jurisdiction anomalies. They were documented findings from actual post-market experience, reflected in a Zoetis-authored regulatory submission bearing actual Health Canada drug identification numbers.

(v) Human Anti-NGF Clinical Experience: The Tanezumab Precedent

Clinical development of the human anti-NGF monoclonal antibody tanezumab raised safety concerns that are directly relevant to evaluating Librela's post-market record.

Tanezumab clinical trials identified a safety signal for rapidly progressive osteoarthritis ("RPOA") — accelerated, structurally destructive joint damage including joint space narrowing, subchondral bone changes, and in severe cases joint collapse requiring total joint replacement.[60] At the March 24–25, 2021 joint meeting of FDA's Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee, the committee voted 19 to 1 against approval of tanezumab.[61]

The following findings from the tanezumab development program are relevant to Librela:

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[58]Original Librela PI; Revised Librela PI

[59]Zoetis Canada Inc., Librela (bedinvetmab injection) Canadian Product Monograph, Drug Identification Number [DIN 02511797] (June 27, 2024) [hereinafter "Canadian Product Monograph 2024"] (Exhibit 10(c))

[60] Berenbaum F, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. *Ann Rheum Dis.* 2020;79:800–810 (Exhibit 12) [hereinafter "Berenbaum et al."]

[61]U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee (Mar. 24–25, 2021), FDA Briefing Document (Exhibit 11(a)) and Meeting Transcript, Transcript at 133 (Exhibit 11(b)) [hereinafter "Tanezumab Advisory Materials"]

First, RPOA was observed in a dose-dependent manner and was identified as a safety concern associated with anti-NGF therapy.[62] Detection of the RPOA signal required systematic multi-year radiographic surveillance involving approximately 18,000 patients and 50,000 radiographs analyzed by 250 experts.[63]

Second, the incidence of RPOA increased in patients receiving long-term NSAID treatment in combination with an anti-NGF monoclonal antibody.[64] The Librela prescribing information expressly references this human clinical finding: "In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody".[65] The label further states: "RPOA has not been characterized or reported in dogs".[66] This data gap is significant in light of the tanezumab clinical experience, in which the incidence of RPOA increased in human patients receiving long-term NSAID treatment in combination with an anti-NGF monoclonal antibody — a finding the Librela prescribing label itself expressly references.[67]

Third, the Librela pre-approval program incorporated no systematic radiographic monitoring with prespecified structural endpoints, and the maximum observation period in the primary field studies was 84 days. By contrast, the tanezumab joint events were detected late in treatment — at a median of 286 days after the first dose and 83 days after the last dose of study medication — and there was 'no evidence that the risk plateaus' with continued dosing past one year. The pre-approval studies were therefore structurally incapable of detecting a signal with this latency.

Fourth, Anti-NGF therapy could also target radiographically healthy joints: of 33 composite joint safety events occurring in joints with normal baseline imaging, 31 were in tanezumab-treated patients and only 2 in NSAID-treated patients. All events of advanced destruction (RPOA2 and osteonecrosis) that developed in healthy joints were in patients treated with tanezumab. Processes presenting with bone destruction and collapse — osteonecrosis and RPOA2 — occurred exclusively in tanezumab-treated patients.[68]

Fifth, FDA's own review team concluded that even the proposed tanezumab REMS would not adequately mitigate the risk.[69] The advisory panel voted 19 to 1 that the REMS would not ensure

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[62]Tanezumab Advisory Materials, Briefing Document at v and vi
[63]*Id.* at 12
[64]Original Librela PI, at Precautions section
[65]SAER at 3-4. (In humans, concurrent NSAID use increases RPOA incidence rates)
[66]Original Librela PI, Precautions section
[67]Original Librela PI, Precautions section; SAER at 3-4
[68]Tanezumab Advisory Materials, Transcript at 73, 208.
[69]Tanezumab Advisory Materials, Briefing Document at 99 (REMS — which included healthcare setting certification, pharmacy certification, patient enrollment, and bilateral X-rays of knees and hips at baseline and annually thereafter) FDA stated: "The Agency is concerned that the proposed REMS will not ensure the benefits of

benefits outweigh risks, citing "no data on how to identify patients before irreversible lesions happen" and the absence of "a monitoring system that one can pick [events] up early enough before the damage is done."[70]

(vi) Summary of FDA's Post-Approval Regulatory Actions

Following Librela's commercial launch, CVM has taken the following post-approval actions:

(a) ***Labeling Revision Recommendation (July 1, 2024)*****:** CVM recommended labeling revisions based on new safety information acquired following drug approval.[71] The revisions added a Post-Approval Experience section listing the following adverse events by body system, in order of decreasing reporting frequency:

- **Neurologic:** ataxia, seizures, paresis, proprioceptive deficits, paralysis
- **General:** anorexia, lethargy, recumbency
- **Renal/Urinary:** polydipsia, polyuria/pollakiuria, urinary incontinence
- **Gastrointestinal:** vomiting, diarrhea
- **Musculoskeletal:** muscle weakness, muscle tremors, lameness
- The section further states: "In some cases, **death (including euthanasia)** has been reported as an outcome of the adverse events listed above".[72]

(b) ***Standard Adverse Event Review (September 10, 2024):*** CVM's Division of Pharmacovigilance and Surveillance completed a comprehensive pharmacovigilance review (DPS-2024-141) covering the period from approval through March 31, 2024.[73] The findings of this review are detailed below.

(c) ***Dear Veterinarian Letter (December 16, 2024):*** CVM issued a Dear Veterinarian Letter notifying practitioners of reported serious adverse events and advising heightened clinical vigilance.[74]

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tanezumab outweigh the risks of RPOA" and noted that "stopping drug after patients develop RPOA2 does not appear to be effective in preventing further damage to the joints."

[70] Tanezumab Advisory Materials, Briefing Document at 99–100

[71] Revised Librela PI, Adverse Reactions section; SAER at 30 (Post-Approval Experience Section (2024))

[72] *Id.*

[73] SAER

[74] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Dear Veterinarian Letter: Adverse Events Reported in Dogs Treated with Librela (bedinvetmab injection) (Dec. 16, 2024) (Exhibit 2) [hereinafter "Dear Veterinarian Letter"]

(d) ***Untitled Letter — Misleading Efficacy Claims (November 20, 2023):*** CVM issued an untitled letter to Zoetis citing false or misleading promotional claims related to Librela's efficacy.[75]

(e) ***Untitled Letter — False and Misleading Advertising (February 5, 2025):*** CVM issued a second untitled letter to Zoetis citing false and misleading advertising related to Librela and other products.[76]

(f) **Client Information Sheet Recommendation:** CVM recommended that veterinarians provide a Client Information Sheet to pet owners prior to Librela administration.[77]

Despite three communication-based interventions (labeling revision, Dear Veterinarian Letter, Client Information Sheet recommendation) and two enforcement actions (Untitled Letters), the adverse event database grew from 3,637 to 16,042 reports — a more than fourfold increase**.**

Timeline: CVM Interventions and Continued Signal Accumulation:

Date	CVM Action/Signal Status
May 5, 2023	Librela approved (NADA 141-562)
July 14, 2023	U.S. commercial launch
Nov 20, 2023	Untitled Letter #1 — misleading efficacy claims
March 31, 2024	SAER data cutoff: 3,637 reports, 458 death outcomes
July 1, 2024	CVM recommends labeling revision (Post-Approval Experience section)
September 10, 2024	SAER published (DPS-2024-141)

[75] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Untitled Letter to Zoetis Inc. re: NADA 141-562, Librela (bedinvetmab injection), Misleading Efficacy Claims, CMS # 665089 (Nov. 20, 2023) (Exhibit 3) [hereinafter "November 2023 Untitled Letter"]

[76] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Untitled Letter to Zoetis Inc. re: NADAs 141-562, 141-546, 141-502, False and Misleading Advertising, CMS # 691206 (Feb. 5, 2025) (Exhibit 4) [hereinafter "February 2025 Untitled Letter"]. CVM found that the Zoetis Petcare YouTube Channel contained multiple Librela videos "purporting to show footage before and after treatment with Librela that contain no risk information, while the visual representations show benefits — such as improved gait or walking — that is clearly attributed to Librela." CVM further found that a Librela television commercial "contain[ed] voice-overs that discuss risk information related solely to the potential for self-injection by veterinary professionals who administer the drug" with "no information in the voice-overs that discusses the risk to the animal although these risks are identified in the PI." CVM concluded these videos were "aimed at the pet owner, yet they omit important safety and risk information for the animal species the drug is approved to treat." This second enforcement action was issued more than fourteen months after the first, during the period of most significant adverse event accumulation

[77] U.S. Food & Drug Admin., Ctr. for Veterinary Med., Librela (bedinvetmab injection) Client Information Sheet (Exhibit 9(c)) [hereinafter "Client Information Sheet"]; SAER at 30: "In addition, we suggest that owners be advised of the adverse reactions that may occur following administration of Librela"

Date	CVM Action/Signal Status
December 16, 2024	Dear Veterinarian Letter issued
January 2025	Revised labeling implemented
February 5, 2025	Untitled Letter #2 — false/misleading advertising
December 31, 2025	Database: 16,042 reports, 2,712 death/euthanasia outcomes
May 2026	UK VMD adds musculoskeletal AEs to SPC; signal continues

(vii) CVM's Standard Adverse Event Review: Findings

CVM's Standard Adverse Event Review ("SAER"), dated September 10, 2024 (DPS-2024-141), represents FDA's own comprehensive pharmacovigilance analysis of the Librela adverse event record. Its principal findings are summarized below.

(a) Scale of the Adverse Event Record

As of April 18, 2024, CVM's database included 3,674 cases reported in association with Librela received through March 31, 2024.[78] Of these, 3,637 were reported in dogs, the species for which the drug is indicated.[79] By a separate FOIA response dated July 11, 2024 covering the period from May 5, 2023 through June 30, 2024, CVM's database contained 6,023 total adverse event reports associated with Librela, of which 5,989 involved dogs.[80] By May 31, 2024 — just two months after the SAER's primary cutoff — CVM's database had grown to 5,301 cases, with the three most reported clinical signs being ataxia, anorexia, and death.[81]

(b) Age Distribution

The age distribution of affected dogs is concentrated in the geriatric population for whom Librela is indicated[82]:

[78]SAER at 10
[79]*Id*.
[80]U.S. Food & Drug Admin., Ctr. for Veterinary Med., Response to FOIA Request re: Librela (bedinvetmab injection) Adverse Drug Event Reports, May 5, 2023 through June 30, 2024 (ADE database search performed July 11, 2024) (Exhibit 14(d)) [hereinafter "July 2024 FOIA Response"]
[81]SAER, Discussion section.
[82]SAER at 10, Table 3.1.1/Figure 3.1.2 Age distribution for Librela.

Age Group	Librela Cases	% of Librela Cases	All Other Products	% of All Other Products
< 1 year	5	0.1%	94,040	10.8%
1 through 5 years	108	3.0%	377,720	43.2%
6 to 10 years	524	14.4%	181,505	20.8%
≥ 10 years	2,652	72.9%	154,450	17.7%
Unknown	348	9.6%	66,358	7.6%

(c) Reporter Type and Veterinarian Suspicion Rates

The SAER documented that 88.9% of Librela cases were reported by a veterinarian (53%) or other health care professional (36%), usually a veterinary technician; only 10% were reported by the animal owner.[83] For all other cases in dogs reported during the same period, 55% were reported by a veterinarian (22%) or other health care professional (32%), and 30% were reported by the animal owner.[84]

The attending veterinarian's level of suspicion for Librela being a causal factor was reported as "probable/high" or "possible/medium" in 80% of cases.[85] It was considered "unlikely/low" in 10% of cases, and in 9% there was no attending veterinarian.[86]

For all other drug products involving dogs during the same period, the attending veterinarian's level of suspicion was "probable/high" or "possible/medium" in 32% of cases, "unlikely/low" in about 5%, and unknown in approximately 45%.[87]

(d) Most Frequently Reported Clinical Signs

The SAER documented that the most frequently reported clinical sign was ataxia, present in 17.4% (634 of 3,637) of all reported cases.[88] CVM noted: "Many of the most frequently reported signs for Librela are not currently on the product labeling, including the most frequently reported sign, ataxia".[89]

[83]SAER at 20
[84]SAER at 21
[85]*Id*.
[86]*Id*.
[87]*Id*.
[88]*Id.* at 12, Table 3.1.4 Most frequently reported clinical signs
[89]*Id.* at 22 ("Many of the most frequently reported for Librela signs are not currently on the product labeling.")

Death was coded as an outcome in 458 cases, representing 12.6% of all reported cases.[90] Other frequently reported unlabeled preferred terms included polydipsia (13.1%), polyuria/pollakiuria (12.7%), muscle weakness (7.4%), convulsion (6.2%), recumbency (5.0%), and paresis (4.9%).[91]

(e) CVM's Response to Sponsor Overreporting Hypothesis

The SAER addressed the sponsor's assertion that elevated reporting was attributable to negative social media activity. CVM concluded:

"CVM does not believe that there is overreporting, as it is generally accepted that underreporting of adverse events is significant in spontaneous reporting systems, including serious or severe adverse drug events and there is no evidence that the cases being reported are not true cases associated with Librela. Current evidence in CVM's database suggests that veterinarians and other health care professionals are involved in most of the cases being reported for Librela."[92]

(f) Disproportionality Analysis

CVM performed disproportionality analysis ("DPA") comparing the relative reporting frequency of specific adverse events for Librela against all other products in the database and against other products approved for control of pain associated with osteoarthritis.[93] The analysis used three algorithms: proportional reporting ratio ("PRR"), information component ("IC") of the Bayesian confidence propagation neural network, and Empirical Bayes geometric mean ("EBGM").[94]

The following severe signs of concern signaled for disproportionality in both the standard and targeted (OA comparator) runs and across the two oldest age-stratified categories[95]:

- Ataxia
- Recumbency
- Polyuria/pollakiuria
- Muscle weakness
- Musculoskeletal disorder NOS
- Paresis
- Proprioception abnormality
- Lameness
- Paralysis

[90] *Id*. at 12, Table 3.1.4 Most frequently reported clinical signs
[91] *Id*.
[92] *Id.* at 21 ("CVM does not believe that there is overreporting")
[93] *Id.* at 22 (Disproportionality Analysis).
[94] *Id.* at 8
[95] *Id*. at 8

- CNS disorder NOS
- Collapse NOS
- Impaired consciousness

CVM noted that "the only labeled sign among those listed above is polyuria/pollakiuria" and that it is "interesting that [lameness] is disproportionately reported compared to other products with the same indication".[96]

Additional signals were identified for focal seizure, epileptic seizure, neuromuscular disorder NOS, death, and other terms.[97] Both ataxia and paresis signaled even in the 1-to-5-year-old age category for both standard and targeted runs indicating the signal is not confined to geriatric dogs and is not explained solely by age-related background pathology.[98]

(g) Case Series Analysis: Causality Assessment and Rechallenge Data

CVM conducted detailed case series evaluations for 13 signs of concern, encompassing 363 individual cases. These 363 cases represent a subset of the 766 qualifying cases with signs of concern; due to the large volume of cases, CVM assessed only those reporting at least two signs of concern for the most frequently reported terms (ataxia, convulsion, lameness, muscle tremor, muscle weakness, paresis, proprioception abnormality, recumbency, and death).[99] Of these, 360 cases (99.2%) received causality scores of 0 or greater, indicating evidence suggestive of at least a possible causal association between the reported signs and Librela.[100]

Eighty cases were assessed as probably associated with Librela, including 7 cases with positive rechallenge on a subsequent dose.[101] The case-by-case breakdown was[102]:

Preferred Term	Cases Probably Associated	Positive Rechallenge
Recumbency	34	5
Ataxia	27	3
Paresis	17	3
Death	26	N/A
Muscle weakness	23	1

[96] *Id.* at 22
[97] *Id.* at 13-14 Table 3.1.6 DPA Results
[98] *Id.* at 13-14 Table 3.1.6 DPA Results
[99] *Id.* at 13-14 Table 3.1.6 DPA Results
[100] *Id.* at 15, Table 3.2.1. Causality assessment summary for signs of concern
[101] *Id.* at 23
[102] *Id.* at 15 Table 3.2.1 Causality assessment summary for signs of concern

Preferred Term	Cases Probably Associated	Positive Rechallenge
Lameness	10	1
Convulsions	7	1
Proprioception abnormality	10	0
Muscle tremor	9	0
Paralysis	3	0
Collapse NOS	3	0

CVM stated: "The evidence is considered stronger in 80 of these cases in which the signs are considered probably-associated with Librela, including 7 cases with positive rechallenge on a subsequent Librela dose".[103]

(h) Time-to-Onset and Dose Number

Two-thirds of the assessed cases reported signs occurring within the first week after Librela administration, with signs occurring within the first day in 30% of cases.[104] Signs occurred after the initial dose of Librela in 70% of cases assessed.[105]

CVM described the commonality across cases: "The narratives of many cases describe the adverse event (or events) occurring within a week of Librela administration, often with no other reasonable explanation for the adverse event in terms of concomitant medication or comorbidities. For cases with dogs on concomitant medications, many indicate a stable dosing history on these other medications prior to introduction of Librela. Many dogs developed the clinical sign or signs of concern after their initial Librela dose. The commonality across cases was that the dogs received a Librela injection".[106]

(i) Concomitant Medication Analysis

No concomitant product use was reported in just over 30% of the 360 assessed cases.[107] Concomitant gabapentin use was reported in 24% (87 of 360) of assessed cases.[108] Regarding ataxia specifically — which is a known side effect of gabapentin — CVM noted that 75% of assessed ataxia cases did not report gabapentin use, stating: "Ataxia is a known side effect of

[103] *Id.* at 23 ("The evidence is considered stronger in 80 of these cases…")
[104] *Id.* at 23-24
[105] *Id.* at 23-24
[106] *Id.* at 23 ("The commonality across cases was that the dogs received a Librela injection")
[107] *Id.* at 24
[108] *Id.*

gabapentin and has been proposed as being responsible for the ataxia seen with Librela use. However, the majority (75%) of the cases assessed for this review do not report gabapentin use".[109] CVM further documented that of the cases reporting concomitant gabapentin use, only one reported gabapentin as treatment for clinical signs occurring after Librela administration and one reported starting gabapentin concurrently with Librela. The remaining cases stated a known or unknown length of time the pet had been on gabapentin prior to Librela administration — indicating that gabapentin was an established, stable medication before Librela was introduced.[110]

(j) Outcomes

At the time cases were evaluated, death (including euthanasia) was reported in 120 of 360 assessed cases (33%), with euthanasia accounting for 89 of those 120 deaths.[111] Recovery was reported in only 38 cases (11%), while 177 cases (49%) were reported as "under treatment".[112]

For convulsion cases specifically, the death rate was 50% (21 of 42), including 16 euthanasias.[113] For paralysis, it was 42% (10 of 24).[114]

(k) Illustrative Case Narratives

> CVM's case series included the following representative narratives; presented in summary form (complete case details are available in CVM's published SAER Exhibit 1):

- A 14-year-old Chihuahua receiving Librela for the first time, with no concomitant medications, experienced 3 seizures within 48 hours of drug administration, continued to decline, and was euthanized 4 days post-administration.[115]
- A 12-year-old Golden Retriever, with no concomitant products, received Librela for the first time. Four days after administration, the patient was laterally recumbent and unable to lift his head. Six days after administration, the patient died.[116]
- A 10-year-old Great Pyrenees, also on Previcox as needed, experienced ataxia about an hour post-administration. Within 24 hours, urinary and fecal incontinence and hindlimb

[109] *Id.* at 24 ("However, the majority (75%) of the cases assessed for this review do not report gabapentin use.")
[110] *Id.* at Discussion section.
[111] *Id. at 24*
[112] *Id.*
[113] *Id.* at 25
[114] *Id.* at 26
[115] *Id.* at 25
[116] *Id.* at 27

lameness developed, progressing to the forelimbs. By 48 hours, the pet was described as paralyzed. Four days post-administration, the pet died.[117]

- A 13-year-old Labrador Retriever, with no concomitant medications, began dragging its hind limbs the same day after receiving its first Librela injection. The same dog experienced hind limb weakness 13 days after receiving its second injection.[118]
- A 9-year-old Saint Bernard receiving its second dose of Librela with no concomitant medications developed acute knuckling and was non-weight bearing on the left forelimb six days post-injection and died nine days post-injection.[119]

(viii) Post-SAER Signal Trajectory

(a) Continued Accumulation Through Q4 2025

As of December 31, 2025, the ADE database has grown to 16,042 reports with 2,712 death/euthanasia outcomes — a more than fourfold increase from the SAER's March 31, 2024 data cutoff. This accumulation occurred just over two and a half years after Librela's U.S. commercial launch during the period in which CVM's communication-based interventions were in effect.[120]

Petitioner conducted an independent analysis of CVM's publicly available adverse event data (quarterly JSON files) through Q4 2025 to assess whether fatal-outcome reports continued to accumulate after the SAER cutoff and after implementation of CVM's communication-based interventions. The analysis reviewed all U.S. Librela adverse event reports with death or euthanasia outcomes, applying standard pharmacovigilance deduplication logic. The methodology is described in Exhibit 13(a), and the charts and supporting summary values are presented in Exhibit 13(b).[121]

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[117] *Id.* at 26

[118] *Id.*

[119] *Id.* at 28

[120] The SAER's data cutoff was March 31, 2024 — approximately nine months after Librela's U.S. commercial launch. CVM's Dear Veterinarian Letter was issued on December 16, 2024, and the revised labeling adding the Post-Approval Experience section was implemented in January 2025.

[121] Gibson J, Analysis of CVM Adverse Drug Event Data for Librela (bedinvetmab injection), Q4 2025 (2026) (Exhibits 13(a)–13(b)) [hereinafter "Gibson Q4 2025 Analysis"]. The analysis uses exclusively CVM's publicly available quarterly adverse event JSON data files. Methodology includes: (a) deduplication based on unique AER identification numbers; (b) "monotherapy" defined as Librela identified as sole drug with no concomitant medications; (c) first-dose versus subsequent-dose classification based on report narrative or onset fields. The methodology is fully described in the methods note accompanying Exhibit 13(a) and is reproducible by any analyst with access to the same public data.

The principal findings are[122]:

Metric	Value
Fatal-outcome reports reviewed (U.S., May 5, 2023 through Q4 2025)	3,440
Individual dogs with death/euthanasia outcomes	3,481
Death outcomes	1,227 (35.2%)
Euthanasia outcomes	2,254 (64.8%)
Median time-to-onset (known-date cases)	3 days
Fatal outcomes within 0–7 days of administration	2,285 / 3,404 (67.1%)
Fatal outcomes reported after first dose	1,880 / 3,481 (54.0%)

These figures are spontaneous-report signal counts derived from CVM's own public pharmacovigilance data; they do not represent incidence rates, relative risk, or determinations of causation.[123]

The charts that follow summarize pharmacovigilance signal counts from FDA/CVM public quarterly adverse event data; they are not incidence, relative-risk, or causation estimates. The current output summaries distinguish reports, unique AER IDs, individual dogs, death outcomes, euthanasia outcomes, death/euthanasia combined fatal outcomes, usable time-to-onset records, first-dose and unknown-dose classifications, and spontaneous-report limitations. The summary files also document reaction-field fatality evidence where the structured outcome field is nonfatal or unknown and separately audit duplicate unique AER IDs.

[122]Gibson Q4 2025 Analysis at Methodology: The data underlying this analysis are derived from CVM's publicly available quarterly adverse event data files. The methodology included: (a) data source as CVM quarterly JSON files downloaded through Q4 2025; (b) deduplication logic based on unique AER identification numbers; (c) definition of "monotherapy" as Librela identified as the sole drug in the ADE report with no concomitant medications listed; (d) criteria for first-dose versus subsequent-dose cases as documented in the report narrative or onset fields; and (e) explicit acknowledgment of the limitations of spontaneous report data for incidence estimation. The methodology is presented in Exhibit 13(a); the charts and supporting summary values are presented in Exhibit 13(b).

[123]*See* FDA, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005) (discussing limitations of spontaneous reporting systems). Spontaneous reports are subject to underreporting, variable data quality, and reporting bias; absence of a denominator precludes incidence calculation.

Figure 13-1. Librela Injectable (All Cases): Death and Euthanasia Outcomes by Quarter

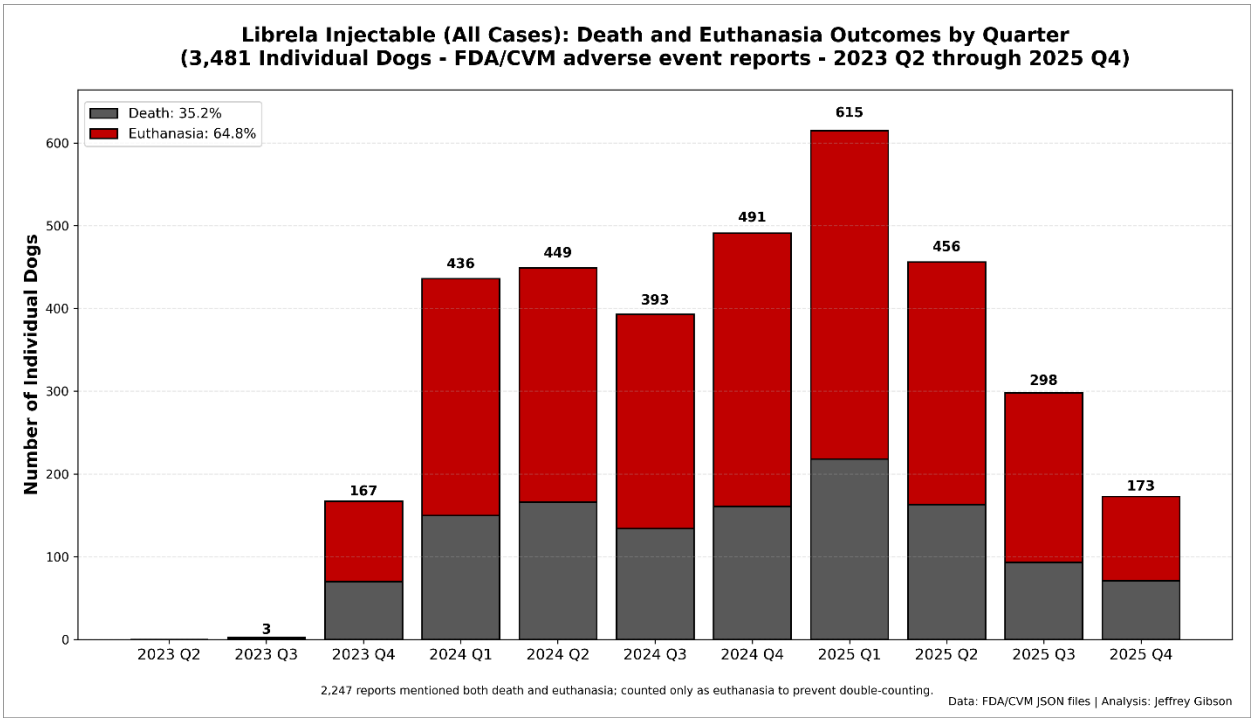

Figure 1. Librela death/euthanasia fatal outcomes by quarter (all cases), 2023 Q2-2025 Q4. Summary source: Librela_All_Cases_Summary.txt (3,440 reports; 3,481 individual dogs; 1,227 death outcomes; 2,254 euthanasia outcomes).

Source: U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) Adverse Event Reporting System (public quarterly JSON files). Analysis and visualization by Jeffrey Gibson, Independent Researcher & Data Analyst, 2026

Figure 13-2. Librela Injectable (Monotherapy): Death and Euthanasia Outcomes by Quarter

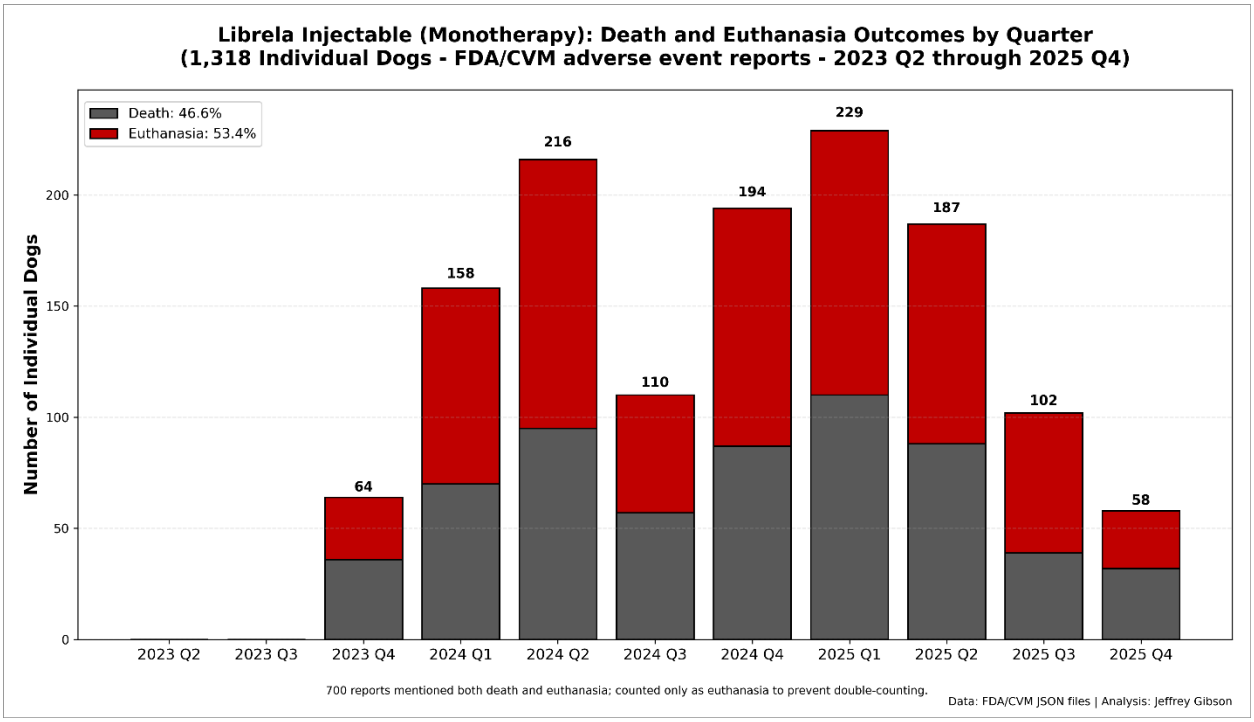

Figure 2. Librela death/euthanasia fatal outcomes by quarter (monotherapy cases), 2023 Q2-2025 Q4. Summary source: Librela_Monotherapy_Summary.txt (1,277 reports; 1,318 individual dogs; 614 death outcomes; 704 euthanasia outcomes).

Source: U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) Adverse Event Reporting System (public quarterly JSON files). Analysis and visualization by Jeffrey Gibson, Independent Researcher & Data Analyst, 2026.

Figure 13-3. Librela Injectable (All Cases): Time to Reported Onset in Fatal Outcome Reports

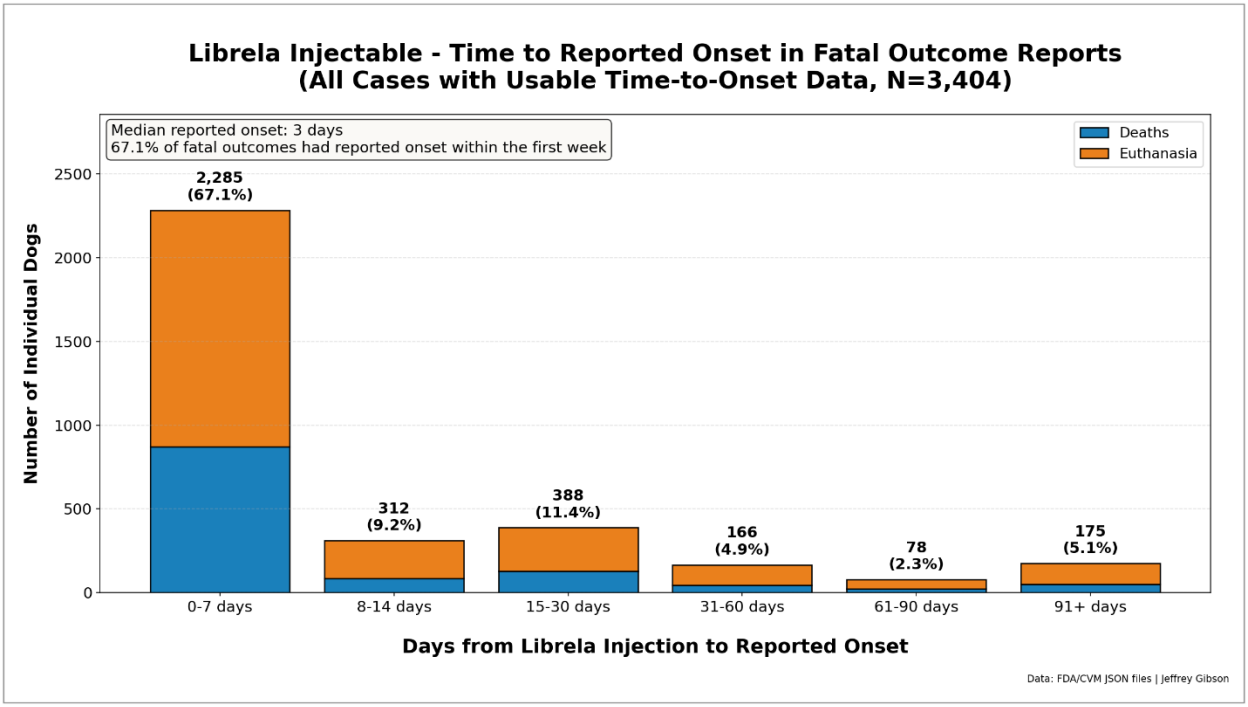

Figure 3. Fatal-outcome time-to-onset distribution (all cases). Summary source: Narrative_Analysis_Summary_All_Cases.txt (3,404 individual dogs with usable time-to-onset data; median reported onset 3 days; 2,285 individual dogs within 0–7 days, 67.1%).

Source: U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) Adverse Event Reporting System (public quarterly JSON files). Analysis and visualization by Jeffrey Gibson, Independent Researcher & Data Analyst, 2026.

Figure 13-4. Librela Injectable (Monotherapy): Time to Reported Onset in Fatal Outcome Reports

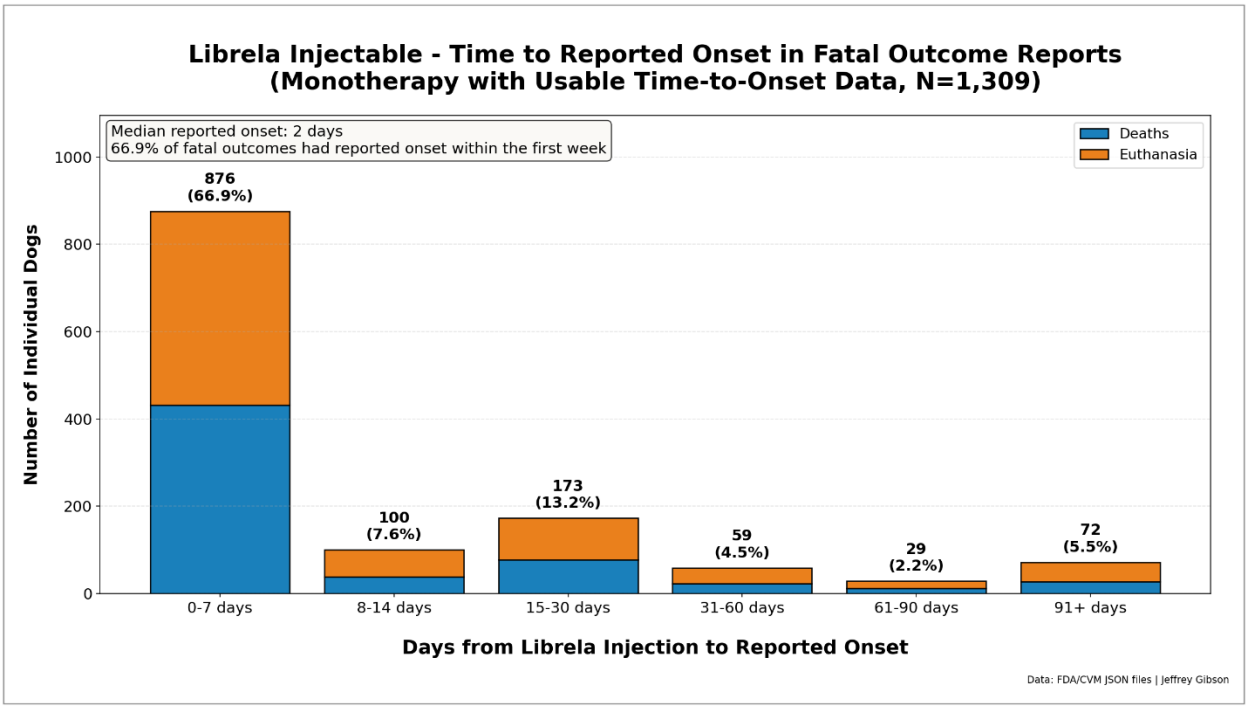

Figure 4. Fatal-outcome time-to-onset distribution (monotherapy cases). Summary source: Narrative_Analysis_Summary_Monotherapy.txt (1,309 individual dogs with usable time-to-onset data; median reported onset 2 days; 876 individual dogs within 0–7 days, 66.9%).

Source: U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) Adverse Event Reporting System (public quarterly JSON files). Analysis and visualization by Jeffrey Gibson, Independent Researcher & Data Analyst, 2026.

(b) Independent Peer-Reviewed Studies Corroborating the Post-Market Signal

1. Farrell et al. (Frontiers in Veterinary Science, May 2025): Musculoskeletal Adverse Events

Dr. Mike Farrell and colleagues published a peer-reviewed study documenting statistically significant musculoskeletal adverse events in Librela-treated dogs.[124] The study found that musculoskeletal adverse events were reported approximately nine times more frequently in Librela-treated dogs than in dogs treated with six comparator osteoarthritis drugs combined.[125]

An independent adjudication panel of 18 board-certified veterinary specialists — including orthopedic surgeons, diagnostic imaging specialists, a human neuro-osteoarthropathy consultant, and a cancer researcher with expertise in monoclonal receptor-based therapeutics — conducted a blinded review of 19 suspected cases.[126] All 18 expert panelists unanimously concluded strong suspicion of a causal association between bedinvetmab and accelerated joint destruction.[127] Inter-rater agreement was substantial ($\kappa = 0.68$), with both diagnostic imaging specialists reporting "very suspicious" of causality in 68% of cases.[128]

Clinical findings included:

- Pathological fractures in 37% of dogs (7 of 19) with no documented trauma[129]
- Joint luxations in 10.5% (2 of 19)[130]
- Destruction of non-index joints (dogs treated for elbow osteoarthritis developed severe hock joint destruction)[131]
- Mean dosing of 12.7 injections, with most adverse events manifesting at least 6 months after treatment initiation[132]
- Histopathological examination excluded inflammatory arthropathy, tick-borne diseases, and neoplasia; findings were described as "similar" to human rapidly progressive osteoarthritis[133]

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[124] Farrell et al. (Frontiers)
[125] *Id.* at 6
[126] *Id.* at 1
[127] *Id.*
[128] *Id.* at 4
[129] *Id.* at 5
[130] *Id.*
[131] *Id.*
[132] *Id.*
[133] *Id.*

Adverse Event Report Translation Errors. Farrell et al. documented systematic discrepancies between adverse event reports filed by attending veterinary specialists and corresponding reports filed by the marketing authorization holder (Zoetis) with regulators. Translation errors were identified in 9 of 19 adjudicated cases (52%), including incorrect diagnoses (n = 5), incorrect severity classifications (n = 5), and incorrect outcome designations (n = 5). The MAH also reported two cases as "overdoses" despite the administered dosages falling within the recommended range. In documented instances, attending specialists reported "suspected RPOA" while the MAH filed reports designating the same cases as "septic arthritis," "non-serious arthritis, recovered/resolving," "non-severe bone and joint disorder, recovered/resolving," or "osteosarcoma." In one case, a 6-year-old Australian Shepherd that developed bilateral stifle joint luxations and fibular fractures following 8 doses of Librela was designated by the MAH as "not serious."[134]

The study also confirmed: "Only 89 dogs received more than three doses [in pre-approval studies], and crucially, no radiographic screening for accelerated joint degeneration was conducted." The authors concluded that "we must rely on post-marketing surveillance to determine whether companion animals experience the adverse joint pathology observed in humans." [135]

2. **Von Pfeil, Armitage, and Nelson (Veterinary and Comparative Orthopaedics and Traumatology, May 2026): Radiographic Characterization of Two Distinct RPOA-Like Phenotypes**

In May 2026, von Pfeil, Armitage, and Nelson published a peer-reviewed case series and mechanistic review in *Veterinary and Comparative Orthopaedics and Traumatology* characterizing the radiographic and histopathological features of suspected bedinvetmab-associated joint pathology in dogs.[136]

The authors identified two distinct clinical presentations of RPOA-like pathology in dogs receiving bedinvetmab.[137] The first pattern involves rapid joint degeneration, instability, and structural collapse occurring after relatively few doses. The second — more insidious — pattern involves fulminant osteophytosis, palisading periarticular periosteal reactions, and heterotopic soft tissue mineralization developing progressively with chronic dosing

[134] *Id.* at 6, 14–15
[135] Dewey & Brunke (Frontiers) at 1
[136] Von Pfeil DJF, Armitage A, Nelson NC. Emerging Signs of Rapidly Progressive Arthritic Changes in Dogs and Cats Receiving Bedinvetmab and Frunevetmab Vet Comp Orthop Traumatol 2026;39:157–161. doi: 10.1055/a-2846-8347 (Exhibit 19) [hereinafter "Von Pfeil, et al (Vet Comp Ortho)"]
[137] *Id*. at 159

(typically more than six monthly injections), masked by the analgesic effect of the drug until advanced structural damage has occurred.[138]

Critically, the authors documented that the canine radiographic phenotype does not align with the characteristic presentation of human RPOA. In human cases, osteophytes are typically minimal or absent; in dogs, the pattern includes severe osteophytosis, palisading periosteal reactions, soft tissue mineralization, bone lysis or erosion, and joint effusion — findings that extend beyond human RPOA and suggest a distinct, potentially more destructive pathophysiology not previously reported with any other analgesic agent across species.[139] International regulatory authorities — including the UK Veterinary Medicines Directorate and Germany's Paul-Ehrlich-Institut — have recognized and are investigating these radiographic findings.[140]

One illustrative case involved a 10-year-old Labrador Retriever that received 18 doses of bedinvetmab for elbow osteoarthritis secondary to elbow dysplasia. Radiographs revealed severe atypical new bone formation extending well beyond articular margins with the appearance of severe, coalescing mineralization of periarticular soft tissues. Arthrotomy revealed intra-articular collections of discrete but coalescing mineralized bodies attached to the synovium by thin fibrous pedicles. Histopathology confirmed a diagnosis of chondro-osseous metaplasia — disorganized islands of cartilage and bone within a matrix of dense fibrous connective tissue.[141]

The article further reported that bedinvetmab prescribed for elbow osteoarthritis resulted in catastrophic structural failure of both tarsal joints — sites with no prior identified pathology — demonstrating that systemic NGF suppression may reduce the threshold for structural failure in any joint undergoing active, even subclinical, degenerative processes, not merely the treated index joint.[142]

Finally, the authors reported emerging evidence of similar pathology in cats treated with the feline anti-NGF monoclonal antibody frunevetmab (Solensia), including a 13-year-old cat that developed severe bilateral tarsal RPOA-like changes after only two doses, with histopathology showing chronic inflammation and synovial hyperplasia similar to human RPOA.[143] This finding supports the conclusion that accelerated joint destruction is

[138] *Id.* at 159-160
[139] *Id.* at 158-159
[140] Von Pfeil, et al. (Vet Comp Ortho) at 159, citing UK Veterinary Medicines Directorate, Summary of Product Characteristics: Librela Solution for Injection for Dogs, Vm 42058/5033, AN: 00241/2026 (revised May 2026; approved May 20, 2026) (Exhibit 18) and Paul-Ehrlich-Institut, Adverse Events and Signal Detection: Bedinvetmab Update (2025).
[141] Von Pfeil, et al (Vet Comp Ortho) at 159
[142] Von Pfeil, et al (Vet Comp Ortho), citing Farrell et al. (Frontiers).
[143] Id. at 159.

a class-wide effect of anti-NGF monoclonal antibody therapy across companion animal species.

The von Pfeil et al. article also referenced a presentation at the Veterinary Orthopedic Society Annual Meeting in March 2026 reporting 38 additional cases of bedinvetmab-associated musculoskeletal adverse events with a mean time to onset of 6.5 months.[144] With the exception of a single case, all dogs received the drug at recommended dosages, frequently in combination with NSAIDs, and developed a subacute, progressive and destabilizing arthropathy characterized by imaging findings including joint laxity, osteophytosis, effusion, and subchondral alterations. Clinical outcomes were frequently severe, with a substantial proportion of affected dogs requiring surgical intervention, and some progressing to euthanasia or limb amputation.[145]

3. Dewey and Brunke (JAVMA, December 2025): Neurobiological Mechanism

Drs. Curtis Dewey and Matthew Brunke published a study in Journal of the American Veterinary Medical Association identifying the neurobiological mechanism that provides a causal explanation for the neurological adverse event profile documented in CVM's SAER.[146] Their analysis established that the cholinergic neurons of the basal forebrain — which depend on retrograde NGF transport for survival and maintenance — are the same neuronal population most vulnerable in dogs with canine cognitive dysfunction syndrome, the recognized canine analog of Alzheimer's disease.[147] In elderly dogs with pre-existing subclinical neurodegeneration, sustained monthly suppression of NGF via a long-half-life monoclonal antibody predictably affects precisely this population.[148]

The post-approval database contains cognitive and mental-status terms consistent with the mechanistic framework described by Dewey and Brunke [149]:

Signal	Number of Reports
cognitive disorder NOS	104
cognitive impairment	42
mental impairment NOS	41

[144] Lee BT, Fox DB. Further characterization of a potential musculoskeletal syndrome associated with bedinvetmab in dogs: Results from a surgeon questionnaire. Paper presented at: Proceedings of the Veterinary Orthopedic Society Annual Meeting; March 14–21, 2026; Big Sky, MT. p. 10.
[145]Von Pfeil et al. (Vet Comp Ortho) at 160–161.
[146]Dewey & Brunke (JAVMA) at 471
[147]*Id.*
[148]*Id*.
[149] January 2026 FOIA Response

Signal	Number of Reports
mental function decreased	14
mental confusion	15

4. **Dewey and Brunke (Frontiers in Veterinary Science, July 2025): Commentary on Musculoskeletal Findings**

In a peer-reviewed commentary responding to the Farrell et al. study, Brunke and Dewey confirmed that the specialist-led disproportionality analysis "reveals a significantly elevated rate of serious musculoskeletal adverse events (MSAEs) — including ligament and tendon injuries, polyarthritis, fractures, musculoskeletal neoplasia, and septic arthritis — in dogs treated with bedinvetmab compared to six other osteoarthritis medications" and that the study "reports expert consensus on a strong suspicion of a causal association between bedinvetmab and accelerated joint destruction."[150] The authors concluded that "the potential for rapid joint degradation and other serious events warrants significant caution" and that "[t]he parallel with adverse outcomes seen in human anti-NGF trials — particularly rapidly progressive osteoarthritis — should not be overlooked."[151] Brunke and Dewey further stated that the adverse event report discrepancies discovered by Farrell et al. "undermine the reliability of the database and may hinder accurate signal detection and pharmacovigilance," and that "[v]eterinarians need assurance that their clinical observations are faithfully recorded and reflected in pharmacovigilance systems" — without which "both animal safety and regulatory accountability are compromised."[152]

(ix) **The Exposure Denominator Problem and Its Implications**

Petitioner acknowledges, consistent with CVM's own disclosures, that spontaneous pharmacovigilance report counts cannot provide incidence estimates without an accurate denominator of treated animals. CVM has correctly noted that "[a]ccumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk, because there is no accurate way to determine how many animals were actually given the drug, which is needed as the denominator in calculations of incidence and relative risk." [153] The absence of an exposure

[150] Dewey & Brunke (Frontiers) at 1
[151] *Id*.
[152] *Id.* at 1, 3
[153] January 2026 FOIA Response at General Information about CVM's ADE Database section ("Accumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk, because there is no accurate way to determine how many animals were actually given the drug, which is needed as the denominator in calculations of incidence and relative risk.").

denominator means that the adverse event report counts documented in this section cannot be used to calculate incidence rates.

However, the absence of a denominator does not diminish the significance of the signal for regulatory purposes. CVM's own validated pharmacovigilance methodology — including disproportionality analysis, case-series causality assessment, and temporal-clustering analysis — was specifically designed to detect safety signals from spontaneous report data without requiring denominator-based incidence calculations, and CVM's SAER applied precisely these methods to reach its conclusions.

(x) Limitations and Unfavorable Information

Pursuant to 21 C.F.R. § 10.30(b)(1), Petitioner discloses the following information and considerations that may be unfavorable to this petition:

(a) Spontaneous reporting limitations*:* Spontaneous adverse event reports are subject to well-documented limitations including underreporting, variable data quality, reporting bias, and the absence of a denominator. Correlation between drug administration and a reported adverse event does not establish causation. These limitations apply to all of the ADE data cited in this petition.

(b) Background disease prevalence*:* The indicated population — geriatric dogs with osteoarthritis — has high background rates of neurologic disease, mobility decline, cognitive impairment, and death from age-related causes. Some proportion of the reported adverse events may reflect natural disease progression rather than drug-related effects. CVM's SAER acknowledged this consideration in its analysis.

(c) Growing exposure*:* Librela's commercial launch and rapid market uptake mean that the absolute number of exposed animals has grown substantially since launch. Increasing absolute report counts are expected as exposure grows, independent of any change in the underlying risk profile. This is why CVM's disproportionality methodology — which controls for differential exposure through database-wide comparisons — is more informative than raw report counts alone.

(d) Weber effect*:* Newly marketed products typically experience elevated reporting rates in their first 1–2 years on market (the "Weber effect"), attributable to heightened prescriber awareness and novelty-driven reporting behavior. Some portion of the elevated reporting for Librela may reflect this expected pattern.

(e) CVM has not formally concluded causation*:* CVM's SAER identified a safety signal and assessed individual case causality, but CVM has not issued a formal determination that bedinvetmab causes the reported neurologic or musculoskeletal

adverse events. CVM's regulatory actions to date have been described as responses to reported adverse events, not as conclusions of established causation.

(f) ***Alternative explanations****:* Concomitant medications (particularly gabapentin, NSAIDs, and other analgesics), pre-existing comorbidities, and age-related decline may account for some proportion of reported events. CVM acknowledged this consideration but noted that 75% of assessed ataxia cases did not report gabapentin use and that over 30% of assessed cases reported no concomitant medications.

(g) ***Therapeutic benefit****:* Librela provides meaningful pain relief for a substantial number of dogs with osteoarthritis. The two field studies demonstrated treatment success rates of 48% (U.S.) and 45.2% (EU) in the treated groups. For dogs that cannot tolerate NSAIDs or other conventional analgesics, Librela may represent the only available pharmacological option for pain management.

Petitioner submits that these considerations, while important context for CVM's evaluation, do not diminish the regulatory significance of the factual record presented above. CVM's own validated analytical methodology was designed to account for the limitations of spontaneous reporting data, and CVM's SAER applied precisely those methods to reach the conclusions documented in Section (vii). The request for enforceable safe-use conditions — rather than withdrawal — reflects Petitioner's acknowledgment that the therapeutic benefit is real and should be preserved for appropriately selected patients

(xi) Summary of the Factual Record

The factual record before CVM consists of the following documented elements:

(a) CVM's own SAER identified positive disproportionality signals across 18 distinct preferred terms, concentrated in the neurologic and musculoskeletal systems.[154]

(b) The attending veterinarian suspicion rate for Librela (80%) is more than double the rate for all other drugs in CVM's database during the same period (32%).[155]

(c) CVM documented 7 positive rechallenge cases among 80 probably-associated cases.[156]

[154]SAER at 6-7 (Disproportionality analysis)
[155]*Id*. at 21
[156]*Id.* at 23

(d) CVM explicitly rejected the sponsor's hypothesis that elevated reporting reflects overreporting due to social media.[157]

(e) The pre-approval studies were 84 days in duration (with a 9-month continuation phase), conducted the target animal safety study in young healthy Beagles without osteoarthritis, and did not incorporate systematic radiographic monitoring or standardized neurologic assessments.[158]

(f) The U.S. pivotal study did not demonstrate a statistically significant difference on its primary effectiveness endpoint at Day 28.[159] Approval rested on a cross-study weight-of-evidence analysis drawing substantially on the EU study.

(g) CVM's SAER identified 458 death-coded outcomes at the March 31, 2024 cutoff.[160] Petitioner's Q4 2025 analysis identifies 3,440 U.S. reports involving 3,481 individual dogs with death/euthanasia fatal outcomes through December 31, 2025.[161]

(h) Independent peer-reviewed studies have documented statistically significant musculoskeletal adverse events consistent with accelerated joint destruction and identified the neurobiological mechanism explaining the observed neurological profile.[162]

(i) International labeling for bedinvetmab disclosed serious adverse events (ataxia, death and seizures) were known adverse reactions prior to U.S. commercial launch.[163]

(j) FDA/CDER's advisory record for the human anti-NGF monoclonal antibody tanezumab documents serious RPOA and joint-destruction safety concerns that the Librela pre-approval program was not designed to evaluate.[164]

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[157]*Id.* at 21

[158]Librela FOI Summary at 7-22 (U.S. and European Field Study design, Margin of Safety Study, Concurrent Use or Exploratory Safety Study)

[159]Librela FOI Summary at 6-7 ("The U.S. study did not demonstrate a significant difference in treatment success at the pre-specified primary endpoint (Day 28)")

[160]SAER at Table 3.1.4 on p 12

[161]Gibson Q4 2025 Analysis (Exhibit 13(b))

[162]Farrell et al., (Frontiers); Von Pfeil DJF, et al. (Vet Comp Ortho);
Dewey & Brunke (Frontiers) and Dewey & Brunke (JAVMA)

[163]European Medicines Agency ("EMA") European Public Assessment Report ("EPAR") materials relating to bedinvetmab (Librela), submitted solely for comparative international regulatory-context purposes. Exhibit 10(a); Canadian Librela Product Monograph and related international labeling materials, submitted solely for comparative international regulatory-context purposes (Exhibit 10(b)-(d))

[164]Tanezumab Advisory Materials, Briefing Document and Transcript

(k) The absence of an exposure denominator — which CVM has authority to address through distribution data requirements under 21 C.F.R. § 514.80(b)(4) — prevents translation of the pharmacovigilance signal into the incidence data necessary for informed clinical decision-making and ongoing regulatory benefit-risk assessment.[165]

B. Legal Background (Authority for Petition and for CVM to Implement the Requested Actions)

The following legal authorities establish the procedural basis for this petition, the statutory and regulatory framework governing the safety of approved new animal drugs, and the specific authorities under which CVM may implement each of the requested actions. These authorities are presented as the legal grounds on which the petition relies. The argument for why these authorities should be exercised in light of the factual record is set forth in Section II. C (Argument) below.

(i) Citizen Petition Procedure and Scope of Available Relief

This petition is submitted under 21 C.F.R. §§ 10.25(a) and 10.30.[166] Section 10.25(a) provides that "[a]n interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."[167] Section 10.30(b)(3) prescribes the citizen petition format and requires "[a] full statement, in a well-organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as representative information known to the petitioner which is unfavorable to the petitioner's position."[168] Petitioner also requests a meeting with CVM staff pursuant to 21 C.F.R. § 10.65(c), which provides that "[e]very person outside the Federal Government may request a private meeting with a representative of FDA in agency offices to discuss a matter" and that "FDA will make reasonable efforts to accommodate such requests."[169]

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[165]SAER at 31

[166]21 C.F.R. §§ 10.25(a), 10.30

[167]21 C.F.R. § 10.25(a) ("An interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."). A petition must be either in the form specified in other applicable FDA regulations or "in the form for a citizen petition in § 10.30." Id. § 10.25(a)(2).

[168]21 C.F.R. § 10.30(b)(3)(B) (Statement of Grounds: "A full statement, in a well-organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as representative information known to the petitioner which is unfavorable to the petitioner's position."); see also id. § 10.30(b)(3)(A) (Action Requested: requiring "the specific action or relief requested" where the petition requests the Commissioner "to take or refrain from taking any other form of administrative action")

[169] 21 C.F.R. § 10.65(c) ("Every person outside the Federal Government may request a private meeting with a representative of FDA in agency offices to discuss a matter. FDA will make reasonable efforts to accommodate such requests.").

Under 21 C.F.R. § 10.30(e)(3), upon review, FDA "may grant or deny the petition, in whole or in part, and may grant such other relief or take other action as the petition warrants."[170] This broad grant-of-relief authority permits CVM to adopt any or all of the measures requested herein, or to fashion alternative relief as warranted by the administrative record subject to substantive authorities discussed below.

(ii) The Statutory Safety Standard for Approved New Animal Drugs

(a) The Affirmative Safety Requirement

Section 512 of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), codified at 21 U.S.C. § 360b, establishes the foundational legal standard governing the safety of new animal drugs.[171]

Under 21 U.S.C. § 360b(a)(1), a new animal drug is deemed "unsafe" for purposes of the FDC Act — and its introduction into interstate commerce is unlawful under 21 U.S.C. § 331(a) — unless:

> (A) there is in effect an approval of an application filed pursuant to subsection (b) with respect to such use or intended use of such drug, "and such drug, its labeling, and such use conform to such approved application."[172]

Before approving any new animal drug application, the Secretary must determine that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof."[173] In making this determination, the Secretary considers, among other factors:

- The probable consumption of the drug and any substance formed because of its use;
- The cumulative effect on man or animal, taking into account any chemically or pharmacologically related substance;
- Safety factors appropriate for the use of animal experimentation data; and
- "Whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice."[174]

The term "safe" as used in Section 512 has reference to the health of man or animal.[175] CVM has consistently interpreted this standard as a relative one: safety is assessed by weighing the severity

[170] 21 C.F.R. § 10.30(e)(3)
[171] 21 U.S.C. § 360b
[172] 21 U.S.C. § 360b(a)(1)(A); see also 21 U.S.C. § 331(a) (prohibiting introduction of adulterated drugs into interstate commerce); 21 U.S.C. § 351(a)(5) (deeming drug adulterated if unsafe under § 360b)
[173] 21 U.S.C. § 360b(d)(1)(A); see also id. § 360b(d)(1)(B) (requiring refusal where test results "do not show that such drug is safe for use under such conditions")
[174] 21 U.S.C. § 360b(d)(2)(A)–(D)
[175] 21 U.S.C. § 321(u) ("The term 'safe' as used in section 360b of this title has reference to the health of man or animal.")

of potential adverse effects, the probability that they will occur, and their reversibility — with the probable benefits of the drug justifying its probable risks under the proposed conditions of use.[176]

(b) T*he Continuous Nature of the Safety Standard*

The requirement that an approved new animal drug be safe under its labeled conditions of use is not a determination made solely at the time of approval. It is a continuous obligation that must be satisfied throughout the product's marketed life. Under 21 U.S.C. § 360b(a)(1)(A), a drug is deemed unsafe unless "such drug, its labeling, and such use conform to such approved application".[177] The post-approval reporting framework at 21 C.F.R. § 514.80 provides the mechanism through which CVM receives information bearing on the continued safety of approved products. It exists to enable CVM to monitor whether this standard continues to be met.[178]

(iii) Authority to Withdraw or Suspend Approval

Section 512(e) of the FDC Act, 21 U.S.C. § 360b(e), provides the Secretary with authority to withdraw approval of a new animal drug application on specified grounds. The grounds relevant to this petition include:

- **(e)(1)(A)** — that "experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved";[179]
- **(e)(1)(B)** — that "new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved";[180]

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[176]FDA, CVM Guidance for Industry #185 (VICH GL43), *Target Animal Safety for Veterinary Pharmaceutical Products* (Apr. 2009), § 5 ("Risk assessment uses the available body of evidence to weigh the severity of an adverse effect (harm), the potential of reversibility, and the probability that it will occur."); *see also* Librela FOI Summary at 24 (stating that Librela "when used according to the label, is safe and effective," reflecting the benefit-risk determination under § 360b(d)).
[177]21 U.S.C. § 360b(a)(1)(A)
[178]21 C.F.R. § 514.80(a)(2)–(3), (b); see also FDA/CVM, Program Policy and Procedures Manual 1240.3525, Review and Assessment of Post-Market Adverse Drug Experience Data (Aug. 15, 2024) [hereinafter "CVM PPM 1240.3525"]
[179]21 U.S.C. § 360b(e)(1)(A)
[180]21 U.S.C. § 360b(e)(1)(B)

- **(e)(1)(C)** — that "on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of."[181]

The statute further provides that if the Secretary "finds that there is an imminent hazard to the health of man or of the animals for which such drug is intended, he may suspend the approval of such application immediately."[182]

Except in cases of imminent hazard, withdrawal proceedings under § 360b(e)(1) require due notice and an opportunity for hearing to the applicant. *See* 21 U.S.C. § 360b(e)(1). This procedural requirement explains why CVM's standard practice — negotiating enforceable post-approval commitments as conditions of continued marketing, rather than initiating formal withdrawal proceedings — is both legally appropriate and administratively efficient.

The withdrawal and suspension authority under § 360b(e) provides the regulatory *leverage* through which CVM may negotiate enforceable post-approval conditions — including post-approval study commitments, enhanced pharmacovigilance requirements, and risk mitigation programs — as alternatives to formal withdrawal proceedings. It is the statutory basis for CVM's authority to act when post-approval evidence raises questions about continued safety.[183]

(iv) Post-Approval Pharmacovigilance and Reporting Requirements

(a) Mandatory Post-Approval Records and Reports

FDA's post-approval pharmacovigilance regulations for approved NADAs and ANADAs are set forth at 21 C.F.R. § 514.80. These regulations impose affirmative obligations on NADA holders:

- Under § 514.80(a)(1)–(2), each applicant must "establish and maintain indexed and complete files containing full records of all information pertinent to safety or effectiveness of a new animal drug" and must "submit reports of data, studies, and other information concerning experience with new animal drugs to the Food and Drug Administration (FDA) for each approved NADA and ANADA." Such records and reports must include "information from domestic, **as well as foreign sources**."[184]

[181] 21 U.S.C. § 360b(e)(1)(C)
[182] 21 U.S.C. § 360b(e)(1) (final sentence)
[183] *See* 21 U.S.C. § 360b(e)(1)–(2); see also ProHeart RiskMAP (Exhibit 15) (demonstrating CVM's use of withdrawal authority to negotiate a comprehensive risk minimization plan as a condition of continued marketing)
[184] 21 C.F.R. § 514.80(a)(1)–(2)

- Under § 514.80(b)(4), applicants must submit periodic drug experience reports containing adverse event data and other safety-relevant information — every six months for the first two years following approval and annually thereafter.[185]
- Under § 514.80(b)(4), applicants must submit distribution data, which provides the denominator-oriented infrastructure for evaluating whether adverse event reporting patterns warrant additional controls.[186]
- Under § 514.80(b)(2)(i), applicants must submit initial reports within fifteen working days for serious and unexpected adverse drug experiences.[187] A "serious" adverse drug experience is one that is fatal, life-threatening, requires professional intervention, or causes prolonged or permanent disability or disfigurement."[188] An “unexpected” adverse experience is one that is not listed in the current labeling.[189] CVM's SAER documented that the most frequently reported adverse events for Librela — including ataxia, paresis, paralysis, and death — were not listed in the original U.S. labeling at launch, meeting the regulatory definition of unexpected adverse experiences.[190]

(b) Authority to Require Enhanced Reporting

Under 21 C.F.R. § 514.80(b)(5)(i), upon written request, "FDA may require that the applicant submit a report required under § 514.80 at different times or more frequently than the timeframes stated in § 514.80."[191] This provision provides CVM with direct regulatory authority to require the enhanced reporting frequency, standardized case narratives, and registry-based submissions described in Requested Action D(iv).

(c) Stated Regulatory Purpose

FDA's stated purpose for the post-approval reporting requirements is to "facilitate a determination under section 512(e) of the act as to whether there may be grounds for suspending or withdrawing approval of the application."[192] This language explicitly links the pharmacovigilance framework to the withdrawal authority at 21 U.S.C. § 360b(e), establishing that the enhanced pharmacovigilance controls requested in this petition serve the same statutory purpose that the reporting framework was designed to advance.

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[185]21 C.F.R. § 514.80(b)(4), (b)(4)(iv) (adverse drug experiences), (b)(4)(v) (summary report of increased frequency of adverse drug experience)
[186]21 C.F.R. § 514.80(b)(4)(i)(A) ("submission of product distribution data including total quantities distributed")
[187]21 C.F.R. § 514.80(b)(2)(i)
[188]21 C.F.R. § 514.3 (definition of "Serious adverse drug experience")
[189]21 C.F.R. § 514.3 (definition of "Unexpected adverse drug experience")
[190]21 C.F.R. § 514.80(b)(2)(i); 21 C.F.R. § 514.3
[191]SAER at 22; Original PI
[192]21 C.F.R. § 514.80(a)(3) (purpose statement); see also FDA/CVM, Program Policy and Procedures Manual 1240.3525, Review and Assessment of Post-Market Adverse Drug Experience Data (Aug. 15, 2024)

(v) Authority for Labeling Revisions, Enhanced Warnings, and Safe-Use Conditions

(a) Misbranding Provisions

FDA's authority to require labeling revisions is grounded in the misbranding provisions of the FDC Act:

- Under 21 U.S.C. § 352(a), a drug is misbranded if "its labeling is false or misleading in any particular."[193]
- Under 21 U.S.C. § 352(f), a drug is misbranded unless "its labeling bears . . . adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users."[194]

(b) Veterinary Prescription Drug Labeling Requirements

For veterinary prescription drugs, 21 C.F.R. § 201.105 sets forth the exemption framework from certain labeling requirements and specifies that such drugs must be restricted to "use by or on the order of a licensed veterinarian."[195] The labeling for such drugs must bear "adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented."[196]

(c) Supplemental Applications for Labeling Changes

Under 21 C.F.R. § 514.8(c)(2), sponsors must submit a supplemental application for major labeling changes — including updates pertaining to effects, dosages, adverse reactions, and contraindications — and must obtain FDA approval prior to distribution of the drug with the revised labeling.[197] FDA recognizes that certain labeling changes "that increase the assurance of drug safety" may be placed into effect prior to approval of a supplemental application in specified circumstances.[198]

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[193] 21 U.S.C. § 352(a)
[194] 21 U.S.C. § 352(f) (adequate warnings clause)
[195] 21 C.F.R. § 201.105(b)(1)
[196] 21 C.F.R. § 201.105(c)(1)
[197] 21 C.F.R. § 514.8(c)(2); *see also* 21 C.F.R. § 514.106 (procedures for approval of supplemental applications)
[198] 21 C.F.R. § 514.8(c)(3); see also CVM Program Policy and Procedures Manual 1243.6020, Review of Abbreviated and New Animal Drug Application Labeling Supplements (NL Subclass) (July 30, 2025), at § II ("changes that increase safety that can be implemented immediately, prior to receipt of written notice of approval")

(d) Use Restrictions in Approved Applications

The statute expressly contemplates that approved applications may include use restrictions to assure safe use. Under 21 U.S.C. § 360b(b)(1)(H), applications must include "the proposed tolerance or withdrawal period or **other use restrictions** for such drug if any tolerance or withdrawal period or other use restrictions are required in order to assure that the proposed use of such drug will be safe" (emphasis added). This express statutory authorization for "other use restrictions" provides the legal basis for CVM to require conditions of use — including prescribing prerequisites, stop rules, and mandatory risk disclosure — as part of the approved application.

(e) Prominent Display Requirements

21 C.F.R. Part 514 further provides that labeling for prescription new animal drugs must include any necessary use restrictions "prominently and conspicuously displayed."[199] While CVM has not historically employed a formal "Boxed Warning" in the same regulatory format prescribed for human drugs under 21 C.F.R. § 201.57(c), the statutory and regulatory authorities available to CVM support imposition of a warning of equivalent prominence and conspicuity.[200] Under 21 U.S.C. § 352(f), labeling must bear adequate warnings "in such manner and form, as are necessary for the protection of users." Under 21 C.F.R. § 514.1(b)(3)(iv), use restrictions must be "prominently and conspicuously displayed." Together, these provisions encompass the authority to require a visually prominent, bordered warning section at the beginning of the prescribing information. Petitioner uses the term "Boxed Warning" to describe a warning displayed with such prominence.

(f) Linkage Between Labeling and Safety

The FDC Act links labeling adequacy to both misbranding and safety status through two independent but complementary mechanisms. First, under 21 U.S.C. § 352(f), a drug is misbranded if its labeling fails to bear adequate warnings "in such manner and form, as are necessary for the protection of users" — a self-executing statutory obligation that applies regardless of what the currently approved application contains.[201] Second, under 21 U.S.C. § 360b(a)(1)(A), a new animal drug is deemed "unsafe" unless "such drug, its labeling, and such

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[199] 21 C.F.R. § 514.1(b)(3)(iv); see also 21 C.F.R. § 201.105(c)(1) (requiring labeling to bear adequate information for use including "any relevant hazards, contraindications, side effects, and precautions")

[200] *See* Labeling Requirements for Approved or Conditionally Approved New Animal Drugs, 89 Fed. Reg. 18,262, 18,272 (Mar. 12, 2024) (proposed rule) (including "Boxed Warnings" in the required content of full prescribing information); see also 21 C.F.R. § 201.57(c)(1) (human drug boxed warning framework, referenced by analogy)

[201] 21 U.S.C. § 352(f)(2) ("adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users").

use conform to such approved application."[202] When post-approval evidence demonstrates that existing labeling no longer supports safe use, CVM may require labeling modifications through the supplemental application pathway;[203] use of the drug inconsistent with such modified conditions would render the drug not in conformity with its approved application — and therefore both adulterated under 21 U.S.C. § 351(a)(5) and unsafe under § 360b(a)(1)(A).[204]

Together, these provisions create a continuous regulatory obligation: as new safety information emerges, CVM must ensure that labeling remains adequate to support safe use under actual conditions of practice, and may employ its withdrawal leverage under § 360b(e) or the supplemental labeling pathway under 21 C.F.R. § 514.8(c) to compel necessary modifications.

Under 21 U.S.C. § 360b(d)(2)(B), the Secretary must consider "the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance." International post-market pharmacovigilance data for the identical compound administered to the same species via the same route is directly relevant to this statutory determination.[205] The Canadian product monograph's pre-launch disclosure of ataxia and seizures as known adverse reactions — based on more than two years of European post-market experience — was available to CVM at the time of U.S. approval.[206]

(g) The Authority Gap: CVM's Own Admission

CVM's December 16, 2024 Dear Veterinarian Letter disclosed that "The FDA Center for Veterinary Medicine does not currently have the authority to mandate safety-related labeling changes."[207] This admission confirms that CVM lacks the express statutory authority available to CDER under 21 U.S.C. § 355(o)(4) to require human drug sponsors to make safety-related labeling changes. CVM's Director testified before Congress on March 30, 2023 that CVM was

[202] 21 U.S.C. § 360b(a)(1)(A)
[203] See 21 C.F.R. § 514.8(c)(2)–(3) (supplemental applications for labeling changes, including safety-enhancing changes that may be implemented prior to written notice of approval)
[204] 21 U.S.C. § 351(a)(5) (drug is adulterated if "unsafe" within the meaning of § 360b); see also 21 U.S.C. § 331(a) (prohibiting introduction of adulterated or misbranded drugs into interstate commerce).
[205] 21 U.S.C. § 360b(d)(2)(B); see also 21 C.F.R. § 514.1(b)(8)(iv) (requiring new animal drug applications to include safety and effectiveness information "from any source, foreign or domestic, including information derived from... commercial marketing experience outside the United States"); 21 C.F.R. § 514.80(a)(1)–(2) (requiring applicants to maintain records of all information pertinent to safety, including information from "foreign sources," and to report such information to FDA)
[206]21 U.S.C. § 360b(d)(2)(B), (D); Canadian Product Monograph (Exhibit 10(c)); see also Librela FOI Summary (U.S. approval date of May 2023)
[207]Dear Veterinarian Letter

"looking to be able to require animal drug sponsors to make post-approval safety related labeling changes based on new safety information that becomes available after approval."[208]

This authority gap does not leave CVM powerless. It means that CVM must exercise its available authorities — including withdrawal leverage under § 360b(e), the "other use restrictions" provision of § 360b(b)(1)(H), and the enhanced reporting authority of § 514.80(b)(5)(i) — to achieve what it cannot accomplish through direct mandate. The ProHeart 6 RiskMAP demonstrates that CVM has previously done exactly this, negotiating comprehensive enforceable conditions as alternatives to formal withdrawal. The same framework applies here.

The citizen petition mechanism under 21 C.F.R. § 10.30 exists precisely to enable formal requests for agency action — including in circumstances where, as here, the Agency has publicly acknowledged constraints on its ability to act unilaterally.

These authorities collectively support the labeling elements described in Requested Action B.

(vi) Authority for Prescribing Prerequisites and Conditions of Use

Under 21 U.S.C. § 352(f), drug labeling must bear adequate directions for safe use, including warnings against use in pathological conditions where use may be dangerous.[209] Under 21 C.F.R. § 201.105(c)(1), prescription animal drug labeling must bear "adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended.[210] Under 21 U.S.C. § 360b(b)(1)(H), the approved application may include "other use restrictions" required to assure safe use.[211]

These provisions authorize CVM to require, as labeled conditions of use:

- Documented diagnostic confirmation of the indicated condition prior to initiation of therapy;
- Baseline clinical assessment and risk screening for identifiable higher-risk populations;
- Longitudinal monitoring requirements, including radiographic follow-up, for continued therapy.

[208]Reauthorization of the Animal Drug User Fee Programs: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce, 118th Cong. (March 30, 2023) (written statement of Tracey Forfa, J.D., Director, FDA Center for Veterinary Medicine) [hereinafter "Forfa Congressional Testimony"] (Exhibit 16).
[209]21 U.S.C. § 352(f)
[210]21 C.F.R. § 201.105(c)(1); see also id. § 201.105(d)(1) (extending the same requirement — including "warnings" — to any labeling distributed by or on behalf of the manufacturer)
[211]21 U.S.C. § 360b(b)(1)(H)

Such conditions operate as enforceable elements of the approved labeling. Use of the drug inconsistent with those conditions would render the drug not in conformity with its approved application and therefore unsafe under 21 U.S.C. § 360b(a)(1)(A).

(vii) Authority for Owner-Facing Risk Disclosure and Client Information Requirements

FDA recognizes "Client Information Sheets" as owner-facing materials that provide safety information about animal drugs, including potential adverse effects and instructions for what to do if they occur.[212] FDA contemplates the use of Client Information Sheets where owner involvement is important for safe and effective use.[213]

Because labeling for prescription veterinary drugs must include adequate information for safe use and may include prominently displayed use restrictions, CVM may operationalize mandatory owner disclosure through labeling-linked requirements. Specifically, CVM may require that the Librela prescribing information state, as an express condition of use under 21 U.S.C. § 360b(b)(1)(H), that the drug shall not be administered without prior provision and documentation of a standardized Client Information Sheet.[214] Because a new animal drug is deemed unsafe unless "such drug, its labeling, and such use conform to such approved application" under 21 U.S.C. § 360b(a)(1)(A), administration without prior provision of the Client Information Sheet would constitute use not in conformity with the approved application — rendering the drug legally unsafe. This approach ties owner disclosure directly to the labeling authority at 21 C.F.R. § 514.1(b)(3)(iv) and to the statutory provision at 21 U.S.C. § 360b(b)(1)(H), which expressly authorizes "other use restrictions" in the approved application to assure safe use.

(viii) Authority over Advertising and Promotional Labeling

FDA's prescription drug advertisement regulation at 21 C.F.R. § 202.1 expressly applies to veterinary prescription drugs and requires that advertisements not be false or misleading and that they include truthful information relating to side effects, contraindications, and effectiveness.[215]

Under 21 C.F.R. § 514.80(b)(5)(ii), sponsors of prescription new animal drugs must submit specimens of advertisements and promotional labeling to FDA at the time of initial dissemination.[216] This provision supports CVM's ongoing oversight of whether Librela's promotion is consistent with the approved labeling and reflects adequate risk disclosure.

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[212]FDA Center for Veterinary Medicine, Client Information Sheets—Take-Home Safety Knowledge, FDA.gov, Animal Health Literacy.
[213]Librela (bedinvetmab injection) Client Information Sheet Frequently Asked Questions about Animal Drugs, FDA.gov
[214]21 U.S.C. § 360b(b)(1)(H)
[215]21 C.F.R. § 202.1
[216]21 C.F.R. § 514.80(b)(5)(ii)

As documented in Section II.A.(vi), CVM has already exercised this authority twice with respect to Librela. CVM issued an untitled letter to Zoetis on November 20, 2023 (Exhibit 3), citing misleading efficacy claims,[217] and a second untitled letter on February 5, 2025 (Exhibit 4), citing false and misleading advertising that omitted animal risk information from owner-directed promotional materials. The persistence of promotional violations across two separate enforcement cycles, spanning more than fourteen months, establishes that voluntary compliance with risk communication standards has been insufficient. This enforcement record provides independent support for the mandatory, standardized owner disclosure requirements requested in Requested Action D.[218]

(ix) Authority to Negotiate Post-Approval Study Commitments and Require Enhanced Reporting

The FDC Act does not contain an express provision authorizing CVM to mandate post-approval clinical studies for approved new animal drugs comparable to the authority enacted for human drugs under 21 U.S.C. § 355(o)(3). The authority supporting post-approval safety study commitments for animal drugs therefore rests on three overlapping — but legally distinct — bases, each with a different scope.

***First*,** under 21 U.S.C. § 360b(e)(1)(A) and (B), the Secretary shall withdraw approval when experience, scientific data, or new evidence shows that the drug is unsafe or is not shown to be safe under approved conditions of use. Where post-market evidence raises serious but not yet conclusive safety questions, CVM may *negotiate* post-approval study commitments — including sponsor-conducted clinical studies, registry enrollment protocols, and radiographic surveillance programs — as conditions of continued marketing authorization, with the withdrawal authority providing the ultimate enforcement mechanism. This is the framework under which the ProHeart 6 RiskMAP post-approval study commitments were established. *See* Section (x) below. Absent sponsor agreement, CVM's recourse is to initiate formal withdrawal proceedings under § 360b(e) — a procedural path that, while more protracted, provides the statutory basis for compulsory action.[219]

***Second*,** under 21 C.F.R. § 514.80(b)(5)(i), upon written request, FDA may require sponsors to submit reports required under § 514.80 at different times or more frequently than the timeframes otherwise specified in the regulations. This provision supports CVM's authority to require

[217]November 2023 Untitled Letter
[218]February 2025 Untitled Letter
[219]21 U.S.C. § 360b(e)(1)(A)–(B). Compare 21 U.S.C. § 355(o)(3) (express authority to require post-marketing studies for human drugs where new safety information emerges), with 21 U.S.C. § 360b (no analogous express provision for animal drugs). In the absence of express post-market study authority, CVM has relied on withdrawal leverage under § 360b(e) to negotiate post-approval study commitments. See Section II.C., infra (discussing ProHeart 6 RiskMAP)

enhanced adverse event reporting frequency — including the accelerated weekly reporting schedules established under the ProHeart 6/12 RiskMAP — and the standardized data collection and outcome reporting elements of Requested Action D.[220]

Third, under 21 U.S.C. § 360b(l)(1), the Secretary may by order require the applicant to establish and maintain records and make reports of data "relating to experience... and other data or information, received or otherwise obtained by such applicant with respect to such drug," where such records and reports are "necessary in order to enable the Secretary to determine... whether there is or may be ground for invoking subsection (e)." This records-and-reports authority supports requirements that the sponsor systematically collect, maintain, and report to CVM specified categories of post-market safety data — including structured outcome data from treated animals — that bear on whether grounds for withdrawal may exist. It does not, standing alone, expressly authorize mandating independent clinical studies or registry enrollment absent the withdrawal-leverage negotiation framework described above.[221]

Together, these authorities provide CVM with the tools to *negotiate or condition continued marketing on* the sponsor-conducted, CVM-supervised post-approval studies described in Requested Action A, and to *directly require* enhanced reporting frequency and structured data collection under the records-and-reports provisions of § 360b(l)(1) and § 514.80(b)(5)(i). CVM's withdrawal authority under 21 U.S.C. § 360b(e) provides the regulatory leverage through which comprehensive post-approval study commitments — including registry enrollment and radiographic follow-up protocols — may be secured as conditions of continued marketing, precisely as CVM did with the ProHeart 6 RiskMAP.[222]
CVM's own leadership has recognized both the importance and the limitations of its post-approval safety tools.[223]

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[220] 21 C.F.R. § 514.80(b)(5)(i); see also id. § 514.80(b)(4) ("Also, FDA may require a report at different times or more frequently."). This reporting-frequency authority is limited to reports already within the scope of § 514.80 and does not independently authorize mandating new categories of clinical investigation.
[221] 21 U.S.C. § 360b(l)(1). This provision authorizes requiring records and reports "necessary in order to enable the Secretary to determine... whether there is or may be ground for invoking subsection (e)." It is a records-and-reports authority that facilitates CVM's ongoing safety determination; it does not constitute an independent post-market study mandate comparable to § 355(o)(3). See also id. § 360b(i) (Secretary may publish "such other information... as the Secretary deems necessary to assure the safe and effective use of such drug")
[222] *See* ProHeart 6/12 RiskMAP (Exhibit 15) (demonstrating CVM's use of withdrawal leverage under § 360b(e) to negotiate comprehensive risk minimization commitments, including post-approval study protocols and accelerated reporting, as conditions of continued marketing); see also 21 U.S.C. § 360b(b)(1)(H) ("other use restrictions... required in order to assure that the proposed use of such drug will be safe").
[223] *See* 21 C.F.R. § 514.80(a)(3) (stating that the post-approval reporting framework exists to "facilitate a determination under section 512(e) of the act as to whether there may be grounds for suspending or withdrawing approval of the application"); CVM PPM 1240.3525, *Review and Assessment of Post-Market Adverse Drug Experience Data* (Aug. 15, 2024) (implementing this framework); Dear Veterinarian Letter at 1 ("The FDA Center for Veterinary Medicine does not currently have the authority to mandate safety-related labeling changes.").

(x) The ProHeart 6 and ProHeart 12 RiskMAP: Established CVM Precedent for Comprehensive Post-Approval Risk Mitigation

The most directly relevant precedent for the relief requested in this petition is CVM's implementation of a comprehensive Risk Minimization Action Plan ("RiskMAP") for ProHeart 6 (moxidectin) and ProHeart 12 (moxidectin). The RiskMAP establishes that CVM has previously exercised the authorities described above to impose structured, enforceable risk mitigation and data collection requirements on an approved animal drug product — and that such measures can be implemented effectively while preserving patient access to the product's benefits.

Background. ProHeart 6 was approved on June 6, 2001, under NADA 141-189[224]. Over the following three years, FDA received 5,913 adverse event reports — including approximately 616 deaths — involving life-threatening events such as anaphylaxis, convulsions, hematopoietic disorders, and hepatopathies, as well as neurologic problems and cardiac signs.[225] The company made three label revisions, added a client information sheet, and issued two Dear Doctor letters at FDA's request during this period.[226]

In 2004, at FDA's request, Fort Dodge Animal Health (subsequently acquired by Pfizer and now part of Zoetis Inc.) voluntarily recalled ProHeart 6 from the U.S. market.[227]

Dr. Stephen F. Sundlof, then-Director of CVM, explained the rationale:

"Despite (our and the company's effort), we have continued to see a high number of adverse events. The thing that was more troubling for us was that the severity of the events was unchanged or going up. We felt that until we have a better understanding of why we were seeing these severe adverse drug reactions, it was prudent to remove the drug from veterinary use."[228]

Dr. Sundlof noted that this was "the first time in his 10 years as director that the center has requested a product recall because of adverse event reports."[229] He further explained that despite

[224]U.S. Food & Drug Administration, Risk Minimization Action Plan (RiskMAP) for ProHeart 6 (moxidectin) & ProHeart 12 (moxidectin) Extended-Release Injectable Suspension, NADA 141-189 & 141-519 (July 2, 2019) (Exhibit 15) [hereinafter "ProHeart 6/12 RiskMAP"]
[225] Kuehn BM, "Fort Dodge recalls ProHeart 6, citing FDA safety concerns", JAVMA News (Oct. 1, 2004) (Exhibit 17) [hereinafter "JAVMA News"]
[226] *Id.* ("The company has made three label revisions, added a client information sheet, and issued two 'Dear Doctor' letters, at the request of the FDA, over the same time period.")
[227]*Id.*
[228]*Id.* ("… we have continued to see a high number of adverse events… it was prudent to remove the drug from veterinary use")
[229]*Id.* ("the first time in his 10 years as director that the center has requested a product recall because of adverse event reports")

administering millions of doses, "the agency and the company have not been able to pinpoint and correct any problems that may exist."[230]

Following recommendations from the January 31, 2005, Veterinary Medicine Advisory Committee meeting, the sponsor conducted additional safety evaluations and modified the manufacturing process.[231] ProHeart 6 was re-introduced to the U.S. market in June 2008 under a comprehensive RiskMAP.[232] ProHeart 12 (NADA 141-519) was subsequently approved on July 2, 2019, and added to the same RiskMAP.[233]

RiskMAP Components. The ProHeart 6 and ProHeart 12 RiskMAP include the following elements, each of which has a direct analog in the relief requested by this petition:[234]

RiskMAP Component	ProHeart 6/12 Implementation	Analogous Librela Request
Product labeling	Approved labels include detailed instructions, precautions, and warnings	Requested Action B
Mandatory veterinarian training and certification	Web-based training and certification required before purchasing or administering product; includes safe use guidelines, adverse reaction recognition, risk factor identification, and reporting requirements	Requested Action D(iii)
Client Information Sheet	Must be provided and reviewed with pet owner before every administration; serves as "a tool for the veterinarian and their staff to facilitate an active conversation with the client"	Requested Actions D(i) and (ii)
Restricted distribution	Available only through certified veterinarians; distributors must verify certification before shipping	Requested Action C and D(iii)
Pre-administration health assessment	"The health of the patient should be assessed by a thorough medical history, physical examination and diagnostic testing as indicated"	Requested Action C(ii)
Enhanced pharmacovigilance	Adverse drug event reports submitted to CVM on a weekly basis; semiannual RiskMAP progress report with summary and analysis of ADE data	Requested Action D(iv)

[230] *Id*. ("the agency and the company have not been able to pinpoint and correct any problems that may exist")
[231] ProHeart 6/12 RiskMAP at 3
[232] *Id.* at 3
[233] ProHeart 6/12 RiskMAP at 3-4; see also U.S. Food & Drug Admin., Ctr. for Veterinary Med., CVM Updates, *FDA Approves ProHeart 12 (moxidectin) for Prevention of Heartworm Disease in Dogs* (July 2, 2019).
[234] ProHeart 6/12 RiskMAP 3-9

RiskMAP Component	ProHeart 6/12 Implementation	Analogous Librela Request
Dear Veterinarian letters	Sent to certified veterinarians when RiskMAP changes occur	Requested Action E
Periodic CVM review	RiskMAP reviewed by sponsor and CVM at intervals of 1–2 years (not to exceed 2 years)	Requested Action A(vi)
Independent Advisory Committee Review (similar to VMAC)	VMAC convened January 31, 2005 and March 24, 2010 in connection with the RiskMAP process	Requested Action F

Effectiveness. CVM has determined that the ProHeart 6 RiskMAP has been effective. The RiskMAP document itself states: "Since the implementation of the RiskMAP for ProHeart 6, there has been a decrease in reports of death associated with anaphylactic reactions relative to estimated exposure. CVM attributes this decrease to implementation of the tools associated with the RiskMAP aimed at mitigating risk; specifically the web-based RiskMAP training and certification program, client information sheet, and adverse drug experience monitoring".[235]

Evolution of the RiskMAP. The RiskMAP was updated in August 2013 based on 4.5 years of post-marketing experience, at which time certain restrictions were relaxed — including the removal of the upper age restriction for first dose and the removal of the requirement for a signed owner consent form — reflecting CVM's assessment that risk had been adequately mitigated.[236] This graduated approach demonstrates that CVM's risk mitigation framework is adaptable: controls can be intensified when warranted by safety data and relaxed when accumulating evidence supports a lower-risk profile.

Legal Basis. The ProHeart 6 and ProHeart 12 RiskMAP measures were not mandated by a specific statutory provision. They were negotiated conditions for continued marketing authorization, supported by CVM's withdrawal authority under 21 U.S.C. § 360b(e).[237] The same authority supports the relief requested in this petition.

The legal significance of this precedent for the relief requested in this petition is addressed in Section II.C.(ix) below.

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[235] *Id. at 3-4*

[236] *Id. at 3*

[237] *Id. at 2–3 (describing voluntary recall at CVM's request and reintroduction under RiskMAP conditions); see 21 U.S.C. § 360b(e)(1)(A)–(B) (providing withdrawal authority that serves as enforcement leverage for negotiated risk mitigation commitments).*

(xi) Authority to Initiate Withdrawal Proceedings

As set forth in Section (iii) above, 21 U.S.C. § 360b(e) authorizes the Secretary to withdraw approval of a new animal drug application when the statutory grounds are met. The post-approval reporting framework at 21 C.F.R. § 514.80 expressly ties FDA's review of post-approval records and reports to "facilitat[ing] a determination under section 512(e) of the act as to whether there may be grounds for suspending or withdrawing approval."[238]

Because a new animal drug is deemed unsafe unless its labeling and use conform to the approved application, 21 U.S.C. § 360b(a)(1)(A), the Secretary's authority under § 360b(e) is implicated whenever post-approval evidence indicates that a drug may no longer be safe under its approved conditions of use.[239] Petitioner's alternative request (Requested Action G) invokes this authority in the event that the enforceable safe-use conditions described in Requested Actions A through F are determined to be infeasible or insufficient to maintain the statutory safety standard.

(xii) Authority for Independent Advisory Committee Convening

FDA's advisory committee regulations at 21 C.F.R. Part 14 authorize the Commissioner to convene advisory committees to provide independent expert input on matters relevant to the safety and effectiveness of regulated products. The Veterinary Medicine Advisory Committee (VMAC) was the advisory body established specifically to advise CVM on matters related to animal drug safety and efficacy.[240] Although VMAC's charter was terminated in 2013, *see* 78 Fed. Reg. 69,991 (Nov. 22, 2013), the Commissioner retains full authority under 21 C.F.R. § 14.40(a) to recharter VMAC or establish a standing or ad hoc advisory committee "whenever it is necessary or appropriate" to review a matter before FDA. Nothing in the FDC Act or CVM's regulations limits this authority to cases involving products that have already been voluntarily withdrawn.[241]

CVM's own precedent establishes that an independent advisory review committee convening is appropriate where a post-market safety signal of significant concern warrants external scientific

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[238] 21 C.F.R. § 514.80(a)

[239] 21 U.S.C. § 360b(e)

[240] 5 U.S.C. §§ 1001–1014 (Federal Advisory Committee Act, as recodified by Pub. L. 117-286 (Dec. 27, 2022)); 21 C.F.R. § 14.1(a)(1) (Commissioner's discretion to convene advisory committee "in the public interest"); 21 C.F.R. § 14.40(a) (establishment or renewal "whenever necessary or appropriate"); 21 U.S.C. § 393(b)(4) (FDA mission carried out "in consultation with experts in science, medicine, and public health"). The Veterinary Medicine Advisory Committee was originally established at 49 Fed. Reg. 28,093 (July 9, 1984) and terminated at 78 Fed. Reg. 69,991 (Nov. 22, 2013). The Commissioner retains authority under 21 C.F.R. § 14.40 to recharter VMAC or establish an ad hoc advisory committee for this purpose.

[241] See 5 U.S.C. §§ 1001–1014 (Federal Advisory Committee Act); 21 C.F.R. §§ 14.1(a)(1), 14.40(a)–(b). VMAC was originally chartered at 49 Fed. Reg. 28,093 (July 9, 1984) and terminated at 78 Fed. Reg. 69,991 (Nov. 22, 2013). The Commissioner's authority to establish or recharter advisory committees under Part 14 is discretionary and requires only a determination that convening is "in the public interest." 21 C.F.R. § 14.1(a)(1)

review. CVM convened VMAC on January 31, 2005 — before allowing ProHeart 6's return to market following voluntary withdrawal — and again on March 24, 2010 to evaluate relaxation of RiskMAP restrictions. [242] Nothing in the FDC Act or CVM's regulations limits the authority to convene a similar ad hoc independent advisory review committee to cases involving products that have already been voluntarily withdrawn.

(xiii) Implications for Pending and Future Anti-NGF Applications

The statutory safety standard at 21 U.S.C. § 360b(d)(1) requires that the Secretary, before approving any new animal drug application, determine that the drug is safe under its proposed conditions of use.[243] Under § 360b(d)(2)(B), the Secretary must consider "the cumulative effect on man or animal of such drug, **taking into account any chemically or pharmacologically related substance**" (emphasis added).[244]

This provision is relevant to any pending or future applications for anti-NGF monoclonal antibody products for companion animals. The post-market safety experience with bedinvetmab, together with the human clinical experience with tanezumab — including FDA/CDER's conclusion that even a comprehensive REMS would not adequately mitigate the anti-NGF RPOA risk[245] — and the published mechanistic literature on NGF's role in neuronal survival and joint homeostasis, constitutes information that is directly pertinent to the safety evaluation of pharmacologically related products.

(xiv) Summary of Legal Authorities Supporting Each Requested Action:

Requested Action	Primary Legal Authority	Supporting Provision
Post-Approval Safety Studies	21 U.S.C. § 360b(e) (withdrawal leverage); 21 C.F.R. § 514.80(b)(5)(i)	21 U.S.C. § 360b(l)(1); § 360b(b)(1)(H); ProHeart 6 precedent
Labeling Revisions/Boxed Warning	21 U.S.C. §§ 352(a), 352(f); § 360b(b)(1)(H); 21 C.F.R. § 201.105	CBE-0 pathway (§ 514.8); Part 514 prominent display
Prescribing Prerequisites	21 U.S.C. § 360b(b)(1)(H); § 352(f); 21 C.F.R. § 201.105	ProHeart 6 pre-administration assessment

[242] ProHeart 6/12 RiskMAP (Exhibit 15) at 2 (referencing January 31, 2005 VMAC meeting); FDA, Veterinary Medicine Advisory Committee Meeting, March 24, 2010 (convened to evaluate ProHeart 6 RiskMAP modifications).
[243] 21 U.S.C. § 360b(d)(1)
[244] 21 U.S.C. § 360b(d)(2)(B)
[245] Tanezumab Advisory Materials, Briefing Document at 100

Requested Action	Primary Legal Authority	Supporting Provision
Owner Disclosure & Enhanced Pharmacovigilance	§ 360b(b)(1)(H); 21 C.F.R. § 514.80(b)(5)(i), (b)(3), (b)(4)	ProHeart 6 CIS; weekly ADE reporting
Updated Communication & Web Resource	CVM established practice; § 514.80 framework	ProHeart 6 Dear Doctor letters
Independent Advisory Review Committee convening	21 C.F.R. Part 14	ProHeart 6/12 VMAC (Jan. 2005, Mar. 2010)
Alternative (Withdrawal)	21 U.S.C. § 360b(e)(1)(A), (e)(1)(B), (e)(1)(C)	§ 514.80(a)(3) purpose statement;
Meeting	21 C.F.R. § 10.65(c)	21 C.F.R. § 10.30(e)(3)

C. ARGUMENT: The Factual Record And Legal Authorities Compel the Grant of Each Requested Action

Introduction

The question before CVM is not whether Librela's post-market safety record warrants concern. Through its Standard Adverse Event Review, its Dear Veterinarian Letter, its labeling revision recommendation, and its two Untitled Letters to Zoetis Inc. (November 20, 2023 and February 5, 2025), CVM has already answered that question. CVM has repeatedly concluded that the post-approval safety experience with bedinvetmab is serious, genuine, and materially different from what the pre-approval studies detected.

The question now is whether the measures CVM has taken to date are sufficient — or whether the continued accumulation of the safety signal after those measures, the independent peer-reviewed corroboration of CVM's findings, and the mechanistic coherence of the adverse event profile now requires the next tier of regulatory response. This petition submits that the issue is no longer whether additional communication is desirable, but whether enforceable safe-use conditions are now necessary to ensure that Librela remains safe under its labeled conditions of use.

These previous measures reflect the Agency's effort to respond to the emerging signal. Petitioner does not criticize those measures. Rather, the continued accumulation of the safety signal following their implementation indicates that the next tier of regulatory action — the graduated, enforceable RiskMAP-based framework that CVM itself pioneered with ProHeart 6 — is now warranted.

The discussion that follows proceeds in two steps. First, it explains why the Librela record has crossed the point at which communication-based measures alone are no longer an adequate regulatory response. Second, it shows why each requested action is a specific, proportionate, and legally available remedy for a specific deficiency in the current conditions of use.

(i) The Evidentiary Record Establishes a Safety Signal of Exceptional Severity, Consistency, and Mechanistic Coherence

Before addressing each requested action individually, it is necessary to establish why the totality of the evidence demands action beyond what CVM has already implemented. The Librela safety signal is not a typical post-market pharmacovigilance finding. It is distinguished by six characteristics that, taken together, place it in a category that communication-based measures alone cannot adequately address.

First, the signal is confirmed by CVM's own authoritative analysis. CVM's SAER identified positive disproportionality signals across 18 distinct preferred terms, concentrated in the neurologic and musculoskeletal systems. CVM's reviewers assessed 363 individual cases in detailed case series evaluations and found evidence suggestive of at least a possible causal association in 360 of them — 99.2%. Eighty cases were assessed as probably associated with Librela, including seven with positive rechallenge. CVM explicitly rejected the sponsor's hypothesis that the signal reflects social media-driven overreporting, finding instead that "there is no evidence that the cases being reported are not true cases associated with Librela" and that "veterinarians and other health care professionals are involved in most of the cases being reported."[246] These are not Petitioner's characterizations. They are CVM's own findings, derived from CVM's own database, using CVM's own validated analytical methodology.

Second, the signal has continued despite CVM's communication-based interventions. At the SAER cutoff of March 31, 2024, CVM's database contained 3,637 adverse event reports and 458 death-coded outcomes. By December 31, 2025, the database had grown to 16,042 reports with 2,712 death/euthanasia outcomes — a more than fourfold increase occurring entirely during the period when CVM's communication-based interventions were in effect.[247]

This growth occurred during a period when CVM had already deployed the Dear Veterinarian Letter, recommended labeling revisions adding a Post-Approval Experience section, and recommended distribution of a Client Information Sheet - the principal communication-based tools available to the Agency. A safety signal that continues after the implementation of risk communication measures warrants evaluation of enforceable safe-use conditions.

[246] SAER at 21
[247] January 2026 FOIA Response

Third, the signal is mechanistically coherent. The adverse event profile is not a random collection of unrelated clinical signs. It is concentrated in precisely the organ systems that the known pharmacology of sustained NGF suppression would predict:

- ***Neurologic events*** (ataxia, paresis, paralysis, seizures, proprioceptive deficits, cognitive decline) are consistent with the established dependence of basal forebrain cholinergic neurons on retrograde NGF transport — the same neuronal population that degenerates in canine cognitive dysfunction syndrome. Dewey and Brunke have published the mechanistic bridge between bedinvetmab's pharmacology and this neurologic vulnerability in the very geriatric population for whom the drug is indicated. Moreover, published research demonstrates that peripheral-only anti-NGF antibodies can disrupt the blood-brain barrier through sympathetic nervous system damage, producing central neurodegeneration even without direct CNS penetration — providing a mechanistic pathway from peripherally administered bedinvetmab to the central neurological events documented post-approval.[248]
- ***Musculoskeletal events*** (accelerated joint destruction, pathological fractures, joint luxations, ligament injuries) are consistent with the class-wide RPOA signal documented in human anti-NGF clinical trials and FDA/CDER's tanezumab advisory record. Farrell et al. have now documented a serious musculoskeletal pattern in Librela-treated dogs, with expert concern regarding causal association.
- ***The irreversibility of exposure*** distinguishes this drug from products where "stop and monitor" labeling can meaningfully mitigate harm. Bedinvetmab's approximately 19-day elimination half-life means that systemic NGF suppression persists for weeks after each injection. There is no reversal agent. CVM's own case narratives document dogs that developed severe neurological signs within hours or days of administration and never recovered — including dogs that were euthanized within days.

Fourth, the signal is corroborated by independent, peer-reviewed expert analysis. The Farrell et al. study documented musculoskeletal adverse events reported approximately nine times more frequently in Librela-treated dogs than in dogs treated with six comparator osteoarthritis drugs combined. An independent panel of 18 board-certified veterinary specialists — including orthopedic surgeons, diagnostic imaging specialists, and a human neuro-osteoarthropathy consultant — unanimously concluded strong suspicion of a causal association between bedinvetmab and accelerated joint destruction. Histopathological findings were described as "similar" to human RPOA. The Dewey and Brunke analysis published in the Journal of the American Veterinary Medical Association identified the specific neurobiological mechanism linking sustained NGF suppression to the neurological adverse events CVM documented. Farrell and his team also documented that the marketing authorization holder

[248] Dewey & Brunke (JAVMA) at 3

mischaracterized the diagnosis, severity, or outcome in 52% of adjudicated cases — filing specialist reports of "suspected RPOA" as "septic arthritis," "non-serious arthritis," or "osteosarcoma" — raising serious questions about the reliability of the sponsor's own pharmacovigilance submissions.[249]

Fifth, the attending veterinarians who treated these animals overwhelmingly believe the drug caused the harm. The veterinarian suspicion rate for Librela — 80% probable or possible — is more than double the 32% baseline for all other drugs in CVM's database. These are not lay opinions. They are the considered clinical judgments of licensed professionals who examined the animals, reviewed their histories, considered the differential diagnosis, and concluded that bedinvetmab was a probable or possible causal factor. When 80% of attending veterinarians reach this conclusion — and when CVM itself has documented positive rechallenge, temporal clustering, and statistical disproportionality — the record provides a strong basis for action.

Sixth, the signal implicates the statutory standard that approved conditions of use be reasonably certain to be followed in practice. Librela is administered in ordinary veterinary practice to elderly dogs with chronic osteoarthritis, often in settings where subtle baseline neurologic deficits, progressive mobility decline, and comorbid disease can blur recognition of treatment-emergent harm unless the label gives clear front-end warnings, prescribing prerequisites, stop rules, and monitoring instructions. The current record therefore does not merely show a serious signal; it shows that the existing conditions of use are not sufficiently operationalized to assure safe use in the real-world population for whom the drug is intended.[250]

These six features lead to a single regulatory conclusion: the Librela record no longer presents a question that can be answered adequately through continued communication alone. It presents a set of concrete deficiencies in the current conditions of use, each of which requires a corresponding corrective measure. Requested Actions A through C address those deficiencies sequentially: first by generating the prospective safety evidence the approval record lacks, second by correcting the inadequacies of the current labeling, and third by imposing front-end prescribing safeguards necessary for safe use in the real-world population.

(ii) Post-Approval Studies Are Necessary Because the Pre-Approval Record Was Not Designed to Detect the Risks Now Being Reported (Requested Action A)

[249] Farrell et al. (Frontiers) at 6, 14-15; Dewey & Brunke (Frontiers) at 1

[250] Petitioner also notes that CVM's disproportionality analysis documented that both ataxia and paresis signaled even in the 1-to-5-year-old age category for both standard and targeted runs. While the geriatric population is most heavily affected — consistent with the mechanistic framework — the presence of signals in younger dogs indicates that the adverse event pattern is not solely explained by age-related background pathology and that the mechanism of harm operates across the lifespan, not exclusively in neurologically compromised elderly animals.

The pre-approval studies for Librela were conducted over 84 days in populations that did not reflect the geriatric, comorbid dogs who constitute the vast majority of the indicated use population. The target animal safety study used young, healthy Beagles without osteoarthritis. No systematic radiographic monitoring was performed. No standardized neurologic assessments were employed. The studies were not designed or powered to detect delayed neurologic decline, progressive structural joint deterioration, or adverse events dependent on cumulative exposure in aging animals.

This is not a criticism of the pre-approval program. It is a statement of its documented design characteristics and their consequences for signal detection. CVM's own SAER implicitly acknowledged this gap: the review identified 18 disproportionality signals for adverse events that were not on the product labeling — including ataxia, the single most frequently reported clinical sign, present in 17.4% of all cases — and noted that "many of the most frequently reported signs for Librela are not currently on the product labeling."[251]

The denominator problem, in turn, explains why post-approval studies are now necessary. Without a defined exposed population, the spontaneous-report system cannot generate incidence estimates, identify relative risk across subgroups, or support the clinical counseling that veterinarians and owners need before initiating a monthly biologic in elderly dogs. The tanezumab precedent shows why that matters: the anti-NGF RPOA signal was detectable only through structured radiographic surveillance over time. Notably, adjudicated joint events were detected at ***a median of 286 days after the first dose***— and there was "no evidence that the risk plateaus" with continued dosing.[252] Hence, as discussed above, Librela's 84-day pre-approval studies were structurally incapable of detecting a signal with this latency.

Librela’s pre-approval program had no comparable surveillance capability, and Farrell and his team now document precisely the sort of accelerated musculoskeletal deterioration that such surveillance was needed to detect. The same gap affects evaluation of alternative explanations. Although concomitant medications such as gabapentin have been cited as possible confounders, CVM found that 75% of assessed ataxia cases did not report gabapentin use, and Petitioner's Q4 2025 analysis identified 1,318 individual dogs with death/euthanasia fatal outcomes in monotherapy cases, with a shorter median time-to-onset than in the broader dataset. The monotherapy subset — in which all concomitant medications are absent by definition — eliminates the most frequently raised confounding explanation, and the shorter median time-to-onset in monotherapy cases (2 days) compared to the broader dataset (3 days) is inconsistent

[251] SAER at 22
[252] Tanezumab Advisory Materials, Briefing Document at 73

with a confounder-driven explanation for the temporal clustering pattern. See Figures 13-1 through 13-4 (Exhibit 13(b)).[253][254]

These data do not establish causation, but they materially weaken the most commonly advanced confounding explanation and reinforce the urgent need for prospective studies capable of controlling for concomitant drugs, defining denominators, and generating the incidence and risk-factor data that the spontaneous reporting system cannot provide.

CVM has both the authority and the precedent to negotiate post-approval study commitments. The post-approval reporting framework at 21 C.F.R. § 514.80 — which expressly ties sponsor reporting obligations to facilitating CVM's determination under § 360b(e) as to whether grounds for withdrawal exist — is the mechanism through which CVM monitors ongoing compliance with the continuous safety standard. The current record satisfies the threshold that the reporting framework was designed to identify.

CVM's own leadership has acknowledged that the Agency's existing post-approval toolkit is insufficient to address emerging safety concerns with the speed and enforceability the public interest requires. In Congressional testimony during the ADUFA V reauthorization hearings in March 2023, CVM Director Tracey Forfa identified the inability to compel sponsors to make post-approval labeling changes as a significant gap in the Agency's authorities and called on Congress to strengthen the post-market safety framework for veterinary drugs.[255] This testimony underscores CVM's recognition that post-approval safety tools, including labeling changes and related safety measures, are an important part of the Agency's statutory mandate. While legislative authority has not yet been enacted, the need Director Forfa identified has only grown more acute. In the absence of direct mandate authority, CVM must use the tools it does have — withdrawal leverage, negotiated conditions of continued marketing, and enhanced reporting requirements — to accomplish what the statute does not yet expressly command. The ProHeart 6 precedent confirms that these indirect tools are adequate to the task.

The requested studies are therefore not exploratory add-ons. They are the minimum prospective safeguards necessary to translate a serious pharmacovigilance signal into the incidence, risk-factor, and outcome data required for responsible prescribing and informed regulatory oversight. Given the age concentration of the signal, the early time-to-onset pattern, the positive rechallenge findings, and the absence of long-term structured surveillance in the approval record,

[253] SAER at 24 and Gibson Q4 2025 Analysis (Exhibit 13(b))
[254]Gibson Q4 2025 Analysis (Exhibit 13(b)), Figures 13-1 through 13-4. Figure 13-2 depicts death and euthanasia outcomes by quarter in the monotherapy subset (1,318 individual dogs; 614 death outcomes; 704 euthanasia outcomes). Figure 13-4 depicts time-to-reported-onset in fatal outcome reports for monotherapy cases (876 known-date dogs within 0–7 days, representing 66.9% of 1,309 dogs with usable time-to-onset data). The monotherapy definition excludes all cases in which any concomitant medication was reported. See Methodology note accompanying Exhibit 13(a).
[255] Forfa Congressional Testimony at 8

Requested Action A is a direct and proportionate response to a now-documented deficiency in the current conditions of safe use.

Requested Action A addresses the evidentiary gap that now impairs informed prescribing and regulatory oversight. Requested Action B addresses the parallel and immediate problem that, even on the basis of the current record, the existing label does not present risk information in the prominence, form, or operational detail necessary for safe use pending generation of those prospective data.

(iii) The Current Labeling Is Inadequate to Ensure Safe Use Under Actual Conditions of Practice (Requested Action B)

Requested Action B is warranted because the current Librela labeling does not provide the prominence, specificity, or operational guidance necessary to ensure safe use under actual conditions of veterinary practice. Under 21 U.S.C. § 352(f), labeling must bear adequate warnings in the manner and form necessary for the protection of users; under 21 U.S.C. § 360b(a)(1)(A), an approved new animal drug remains safe only if its labeling and use conform to the approved application. When the post-approval record demonstrates that existing labeling no longer adequately communicates the product's material risks or the conditions necessary for safe use, CVM has both the authority and regulatory basis to require corrective revision.

The current Librela prescribing information, even as revised in January 2025, remains inadequate in four critical respects.

First, the current presentation of post-approval risk information lacks the prominence necessary to support safe prescribing. The most serious risks documented in the post-approval record—including ataxia, death coded as an outcome, positive rechallenge, and an 80% veterinarian suspicion rate—appear only in a later section of the prescribing information, after the pre-approval adverse reactions table. In actual practice, veterinarians consulting the label before an initial dose are more likely to encounter the pre-approval adverse-reaction profile first: urinary tract infection, bacterial skin infection, dermatitis, and other comparatively routine events. The post-approval signals that CVM itself identified as serious are therefore disclosed, but not in a manner commensurate with their severity or with the decisions prescribers must make before dosing. For a product administered monthly to an elderly, clinically vulnerable population, that lack of visual prominence is a material labeling deficiency.

The need for stronger warning prominence is reinforced by the product's effectiveness record. FDA approved Librela based on the totality of the evidence, but the U.S. pivotal field study did not independently demonstrate a statistically significant difference on its primary effectiveness endpoint at Day 28, and approval depended substantially on the broader weight-of-evidence analysis. This point is relevant not to relitigate approval, but to inform the current benefit-risk

assessment as CVM evaluates whether existing labeling and conditions of use remain adequate in light of the post-approval safety record. Where the benefit side of the balance was already qualified and the risk side has since become substantially more serious, stronger front-end warning language is warranted.

Under 21 U.S.C. § 360b(a)(1), the probable benefits must justify the probable risks. CVM itself characterized Librela as "a veterinary drug in a novel therapeutic class" in its November 2023 Untitled Letter[256]— a characterization that heightens, rather than diminishes, the standard of caution warranted in post-market labeling. The current labeling framework for Librela—without a prominently displayed boxed or equivalently conspicuous warning, without labeled stop rules, without prescribing prerequisites, and without standardized owner disclosure—no longer adequately supports a safe-use benefit-risk balance under actual conditions of practice. A moderate, evidence-qualified effectiveness finding does not justify a serious, multi-system adverse event profile including fatal outcomes in monotherapy cases, without enforceable conditions of use designed to identify appropriate patients, enable early detection of harm, and ensure informed owner decision-making.

Second, the labeling fails to provide operational stop rules necessary to prevent avoidable repeat exposure after serious warning signs emerge. The current label identifies certain reported adverse events, but it does not tell veterinarians when dosing must stop, when urgent evaluation is required, or when re-dosing is contraindicated. A clinician who observes new-onset ataxia, paresis, collapse, seizure activity, or rapid structural deterioration in a Librela-treated dog is given no explicit labeled instruction to withhold the next dose or to discontinue treatment pending evaluation. That omission is especially significant because CVM documented positive rechallenge cases in which adverse events recurred upon re-administration. Where the post-approval record shows that repeat exposure may reproduce or worsen serious harm, labeling that lacks clear stop rules and re-dosing prohibitions is not adequate to assure safe use.

Third, the labeling does not adequately address the specific risk profile of the geriatric population that constitutes the product’s core use population. CVM’s SAER documented that 72.9% of adverse event cases occurred in dogs aged 10 years or older—the very population for whom Librela is most commonly prescribed. The mechanistic literature now provides a biologically coherent explanation for that concentration: age-related vulnerability of the basal forebrain cholinergic system and the broader effects of sustained NGF suppression in elderly animals with preexisting degenerative disease. Yet the current labeling contains no geriatric-specific warning language, no enhanced screening guidance, and no tailored monitoring recommendations for the population in which the signal is most concentrated. A labeling

[256] November 2023 Untitled Letter at 1

framework that treats geriatric dogs and younger adults as functionally equivalent does not reflect the risk profile documented in the post-approval record.

Fourth, the current labeling no longer adequately addresses the RPOA-related risk and should be revised accordingly. The current label acknowledges the human anti-NGF experience only in highly qualified terms, stating that rapidly progressive osteoarthritis ("RPOA") has not been characterized or reported in dogs. That formulation is no longer sufficient in light of the accumulated record. The tanezumab advisory record established that RPOA is a class-relevant anti-NGF safety concern detectable only through structured surveillance, and Librela's own pre-approval program did not include the systematic radiographic monitoring necessary to detect it. Post-approval, Farrell et al. have now documented musculoskeletal adverse events in Librela-treated dogs that expert reviewers considered strongly suspicious for accelerated joint destruction, including pathological fractures, joint luxations, and destruction of non-index joints. In these circumstances, labeling that continues to frame the issue primarily as an absence of characterization understates the practical risk to prescribers and owners and fails to provide the caution necessary for safe use.

Taken together, the post-approval record demonstrates that Librela's current labeling is not sufficient in prominence, content, or clinical usability to assure safe prescribing under actual conditions of practice. The combination of serious neurologic outcomes, fatal outcomes, positive rechallenge, geriatric concentration, and emerging musculoskeletal evidence provides a strong basis for CVM to conclude that prominent warning revision, explicit stop rules, and related labeling changes are warranted.

Requested Action B addresses the immediate inadequacy of the current label. Requested Action C addresses the parallel point-of-care problem that risk cannot be managed safely if treatment is initiated without confirming the indication, documenting baseline status, and reassessing the patient before repeat exposure.

(iv) Prescribing Prerequisites Are Necessary to Align Treatment Initiation with Confirmed Indication and Safe-Use Conditions (Requested Action C)

Requested Action C is warranted because the current post-approval record demonstrates that safe use of Librela depends not only on what veterinarians are told after dosing decisions are made, but also on what must be confirmed, documented, and assessed before treatment is initiated and before each subsequent dose is administered. Under 21 U.S.C. § 360b(b)(1)(H), CVM may require "other use restrictions" necessary to assure safe use, and under 21 U.S.C. § 352(f) and 21 C.F.R. § 201.105, prescription animal drug labeling must provide the information and conditions necessary for safe veterinary use. Where the adverse event profile is concentrated in the musculoskeletal and neurologic systems, and where many serious outcomes arise rapidly after an

initial dose, baseline qualification and interval reassessment are not optional refinements; they are core conditions of safe prescribing.

The current labeling permits any veterinarian to administer Librela to any dog based on a clinical impression of osteoarthritis, without requiring diagnostic confirmation, baseline neurologic assessment, or documentation of risk factors for serious adverse events. This is not consistent with safe use of a drug whose adverse event profile is concentrated in the musculoskeletal and neurological systems, whose indicated population consists predominantly of geriatric animals with high rates of comorbidity, and whose mechanism of action involves sustained suppression of a neurotrophic factor essential for neuronal survival and joint homeostasis.

First, Librela should not be initiated without documented confirmation that the dog in fact has osteoarthritis appropriate for treatment with an anti-NGF monoclonal antibody. CVM approved Librela for the control of pain associated with osteoarthritis in dogs, not for undifferentiated mobility decline, generalized weakness, or poorly characterized geriatric dysfunction. In actual practice, however, the population receiving Librela is elderly and frequently medically complex, and the differential diagnosis for impaired mobility in that population includes not only osteoarthritis, but also neurologic disease, myelopathy, vestibular dysfunction, cognitive decline, joint instability, fracture, neoplasia, and other conditions for which Librela may be ineffective, inappropriate, or actively misleading in its symptomatic effect. Requiring documented confirmation of osteoarthritis before first dosing would better align real-world prescribing with the approved indication and establish the structural baseline necessary for later evaluation of accelerated joint pathology.

Second, baseline neurologic assessment and risk screening are necessary because the post-approval signal is concentrated in exactly the domains that can be obscured in an untreated elderly dog if they are not documented at the outset. CVM's SAER found that 72.9% of adverse event cases occurred in dogs aged 10 years or older, and both the SAER and the published literature identify neurologic signs—including ataxia, paresis, proprioceptive deficits, collapse, and cognitive decline—as major features of the emerging safety profile. Without a documented baseline examination, clinicians cannot reliably distinguish new treatment-emergent deficits from preexisting gait abnormality, hind-limb weakness, vestibular dysfunction, or age-related cognitive impairment. A baseline neurologic screen, relevant comorbidity review, and risk-factor assessment therefore serve not as burdensome formalities, but as the minimum clinical groundwork for recognizing change after exposure to a long-half-life biologic whose effects are not readily reversible.

Third, continued therapy should be conditioned on documented reassessment before each subsequent dose. CVM's own data show that many serious events occur within days of administration and that positive rechallenge has occurred upon re-exposure. In that setting,

monthly dosing cannot be treated as a routine refill decision. Each subsequent administration should follow documented review of neurologic status, mobility, interval adverse signs, and any new lameness or functional decline, with defined triggers for further evaluation and for withholding treatment. This is especially important where the product is used chronically, where long-term safety beyond nine months remains uncharacterized, and where the absence of clear baseline and follow-up documentation makes meaningful pharmacovigilance more difficult. Conditioning continued dosing on interval reassessment is therefore a direct and proportionate response to the risks documented in the post-approval record.

Fourth, radiographic documentation of the treated joint(s) should be required at baseline and at defined intervals during continued therapy because it is the only available method to detect the accelerated joint destruction that is the hallmark adverse effect of anti-NGF therapy across species. The tanezumab clinical program — involving approximately 18,000 patients and 50,000 radiographs analyzed by 250 experts — demonstrated that RPOA is detectable only through structured radiographic surveillance over time; it cannot be identified by clinical examination alone because NGF inhibition masks the pain that would otherwise alert the clinician to progressive structural damage.[257]

This creates a uniquely dangerous pharmacological paradox: bedinvetmab's therapeutic mechanism of action — suppression of the NGF-mediated pain signal — is the same mechanism that actively prevents clinical detection of the structural joint destruction it may be causing. Von Pfeil et al.'s identification of an "insidious" second phenotype, in which fulminant osteophytosis and periosteal reactions develop progressively over six or more monthly doses "masked by the analgesic effect of the drug until advanced structural damage has occurred,"[258] confirms that the drug's pain-masking effect renders the veterinarian clinically blind to ongoing joint destruction — making radiographic monitoring the only available safeguard against irreversible harm.[259]

Farrell et al. confirm that this surveillance gap exists for Librela: "Only 89 dogs received more than three doses, and crucially, no radiographic screening for accelerated joint degeneration was conducted" in the pre-marketing clinical trials.[260] The same authors observe that "Zoetis was unable to self-report accelerated joint destruction due to the absence of radiographic

[257] Roemer FW, et al., Role of imaging for eligibility and safety of a-NGF clinical trials, Ther Adv Musculoskeletal Dis 15:1–11 (2023); Guermazi A, et al., Osteoarthritic Imaging 2(3-4):100082 (2022)
[258] Von Pfeil, et al. (Vet Comp Ortho) at 155–56 (Exhibit 6) (identifying "two distinct clinical presentations": (1) rapid joint degeneration after relatively few doses, and (2) progressive osteophytosis developing over six or more monthly injections, "masked by the analgesic effect of the drug until advanced structural damage has occurred")
[259] This pharmacological paradox distinguishes anti-NGF monoclonal antibodies from all prior veterinary analgesics: NSAIDs and other pain medications reduce pain but do not eliminate the NGF-mediated protective signaling pathway that alerts both the animal and clinician to progressive structural deterioration. See Dewey & Brunke (JAVMA) at 3 (Exhibit 7) (describing NGF's role in nociceptive signaling and the consequences of its suppression)
[260] Farrell, et al. (Frontiers) at 9

investigations" and that "we must rely on post-marketing surveillance to determine whether companion animals experience the adverse joint pathology observed in humans."[261]

The Farrell et al. expert panel — comprising 18 specialists who reviewed 19 dogs with suspected musculoskeletal adverse events — "unanimously concluded a strong suspicion of a causal association between bedinvetmab and accelerated joint destruction."[262] Notably, 13 of 19 cases manifested at least 6 months after Librela initiation, and multiple cases involved dogs with documented pre-treatment imaging showing mild or moderate OA that progressed to pathological fractures, joint luxations, or subchondral osteolysis during treatment.[263] Without baseline radiographs, these cases would have been indistinguishable from natural OA progression — exactly as occurred in the tanezumab program before structured surveillance was mandated.

Requiring radiographic documentation at baseline and at clinically appropriate intervals (e.g., every 6–12 months during continued therapy) serves three functions: (a) it confirms the OA diagnosis and excludes pre-existing conditions that contraindicate NGF inhibition; (b) it establishes a structural baseline against which accelerated deterioration can be measured; and (c) it provides the radiographic data necessary to support the post-approval studies requested in Requested Action A. This requirement directly parallels the risk mitigation approach that the FDA mandated for the tanezumab program after voting 21–0 to recognize RPOA as a side effect of anti-NGF monoclonal antibodies.

FDA's own review team concluded that even a comprehensive REMS for tanezumab — including baseline and annual bilateral radiographs, healthcare setting certification, and patient monitoring — would not adequately mitigate the RPOA risk, finding "no clear evidence to support that requiring and implementing the proposed elements will have an impact on preventing or the progression of RPOA."[264] If a full REMS was deemed insufficient to mitigate anti-NGF RPOA in humans receiving structured clinical trial monitoring, the complete absence of radiographic surveillance for Librela in veterinary practice is a manifest deficiency in the current conditions of use.

In fact, the statute expressly contemplates this type of condition. Under 21 U.S.C. § 360b(b)(1)(H), approved applications may include "other use restrictions" necessary "to assure that the proposed use of such drug will be safe." Diagnostic confirmation and baseline assessment are precisely the type of use restrictions that this provision authorizes. The ProHeart 6 and ProHeart 12 RiskMAP established CVM's precedent for requiring pre-administration

[261] *Id.* at 9
[262] *Id.* at 9
[263] *Id.* at 9
[264] Tanezumab Advisory Materials, Briefing Document at 100

health assessment, including "a thorough medical history, physical examination and diagnostic testing as indicated," as a condition of continued marketing.[265]

Requested Action C does not seek to restrict access arbitrarily. It seeks to ensure that Librela is prescribed to appropriately qualified patients, with a documented baseline and clinically meaningful reassessment before repeat exposure. For a drug administered monthly to a geriatric population, associated in the post-approval record with serious neurologic and musculoskeletal outcomes, and not readily reversible once given, those prerequisites are not extraordinary. They are the ordinary clinical safeguards that the current record now shows are necessary to assure safe use under actual conditions of veterinary practice.

(v) Standardized Owner Disclosure and Enhanced Pharmacovigilance Are Necessary to Ensure Informed Decision-Making and Generate Interpretable Safety Data (Requested Action D)

Requested Action D is warranted because Librela's current safety framework depends heavily on what occurs after the dog leaves the clinic, yet the existing system does not require standardized owner disclosure, documented acknowledgment, or enhanced sponsor reporting sufficient to convert owner-observed events into reliable regulatory data. Many of the most serious reported outcomes—ataxia, collapse, recumbency, seizure activity, sudden lameness, rapid decline, and death or euthanasia—develop at home within days of administration. If owners are not consistently informed what to watch for, when to seek urgent care, and that further dosing may need to stop, the practical effectiveness of any warning or prescribing safeguard is sharply reduced.

The current Client Information Sheet recommended by CVM was a necessary first step. But a recommended, non-standardized handout — without documented acknowledgment that it was provided and reviewed — is not sufficient to ensure that owners actually receive the information necessary for informed consent, particularly for a drug with irreversible exposure and an adverse event profile of this severity.

The ProHeart 6 and ProHeart 12 RiskMAP established CVM's precedent for mandatory Client Information Sheet distribution before every administration, describing the CIS as "a tool for the veterinarian and their staff to facilitate an active conversation with the client prior to administration." The severity of Librela's documented safety profile — which includes a substantially higher death-to-case ratio and a broader range of serious organ-system-specific

[265] ProHeart 6/12 RiskMAP

adverse events than ProHeart 6 at the time of its voluntary withdrawal — warrants at least equivalent owner-facing risk communication controls.[266]

The necessity of mandatory, standardized risk disclosure is further supported by CVM's own enforcement record. CVM issued Untitled Letters to Zoetis on November 20, 2023 and February 5, 2025 — finding false and misleading efficacy claims and inadequate risk disclosure in promotional materials, respectively. The second Untitled Letter was issued more than fourteen months after the first, after the Dear Veterinarian Letter had already been distributed, while the adverse event database continued to grow. The persistence of promotional deficiencies across two separate enforcement cycles, spanning the period of most significant adverse event accumulation, establishes that voluntary compliance with risk communication standards is insufficient. Mandatory, standardized owner disclosure — with documented acknowledgment — is the appropriate response to a documented pattern of inadequate voluntary risk communication.

The pattern of sponsor information management extends beyond promotional materials. Farrell et al. documented that in 52% of adjudicated musculoskeletal cases, the marketing authorization holder filed adverse event reports with regulators that mischaracterized the attending specialist's diagnosis, severity assessment, or outcome designation — including filing reports of "suspected RPOA" as "septic arthritis" or "non-serious arthritis, recovered/resolving."[267] Dewey and Brunke stated that these discrepancies "undermine the reliability of the database and may hinder accurate signal detection and pharmacovigilance."[268] A CVM-auditable registry with standardized fields — rather than continued reliance on sponsor-mediated report submissions — is the necessary corrective.

Enhanced pharmacovigilance controls are equally necessary. The current spontaneous reporting system, while critical for signal detection, cannot generate the denominator-based data necessary for informed clinical decision-making. As documented in Section II.A(ix), CVM has acknowledged that spontaneous reporting data cannot generate incidence estimates without an exposure denominator — a limitation that underscores the need for the denominator-based surveillance infrastructure requested herein.[269] A sponsor-administered registry with standardized exposure and outcome data — auditable by CVM, with periodic summary submissions — would begin to address this fundamental limitation. The ProHeart 6 RiskMAP required weekly adverse event report submissions and semiannual summary analyses.

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[266] JAVMA News (at the time of withdrawal, there were 616 deaths).
[267] Farrell et al. (Frontiers) at 6, 14-15
[268] *Id*. at 1
[269] January 2026 FOIA Response at General Information about CVM's ADE Database section ("Accumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk, because there is no accurate way to determine how many animals were actually given the drug, which is needed as the denominator in calculations of incidence and relative risk.").

Comparable or more frequent reporting for Librela is warranted by the scale and severity of the documented signal.

Under 21 U.S.C. § 360b(d)(2)(B), FDA must consider "the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance." International post-market pharmacovigilance data for the identical compound administered to the same species via the same route is directly relevant to this analysis. The failure to incorporate the European and Canadian post-market experience — including the Canadian product monograph's disclosure of ataxia and seizures as known adverse reactions — into the U.S. labeling at launch raises an independent misbranding concern under 21 U.S.C. § 352(a) and (f). The adverse events that now dominate the U.S. post-approval signal were documented known adverse reactions in Canada before U.S. commercial launch.

Under 21 C.F.R. § 514.80(a)(1)–(2), Zoetis was obligated to establish and maintain records of all information pertinent to safety — including information from **"foreign sources"** — and to report such information to FDA. The October 2022 Canadian label constitutes precisely such foreign-source safety information. The adverse events now dominating the U.S. post-approval record — and which CVM identified in its SAER as the most frequently reported, unlabeled preferred terms — were disclosed as known post-market findings in a Zoetis-authored Canadian regulatory document seven months before the U.S. label was approved. FDA should formally examine whether the October 2022 Canadian adverse reaction disclosures — and the underlying pharmacovigilance data that supported them — were fully and accurately disclosed to CVM in connection with the U.S. NADA review, and whether the omission of ataxia, death, and the other Canadian-labeled adverse reactions from the U.S. label at launch is consistent with Zoetis's foreign-source reporting obligations under 21 C.F.R. § 514.80(a). The failure to incorporate this international experience into U.S. labeling at launch raises an independent basis for finding the current labeling inadequate under 21 U.S.C. § 352(a) and (f).

Standardized owner disclosure and documented acknowledgment are therefore not ancillary consumer-information measures. They are core safe-use conditions for a monthly administered biologic whose clinically significant adverse signs often emerge between visits and whose pharmacologic effects are not readily reversible once administered. A CVM-reviewed Client Information Sheet, coupled with written acknowledgment retained in the medical record, would help ensure that every owner receives the same minimum safety information before first dosing and would provide an auditable mechanism for implementation—precisely the type of operational safeguard CVM previously used under the ProHeart RiskMAP.

The same reasoning supports enhanced pharmacovigilance. CVM’s own record confirms a serious signal, but the spontaneous-report system still leaves critical gaps in incidence estimation, dose-specific exposure assessment, subgroup risk analysis, and outcome tracking.

Requested Action D responds directly to those gaps by pairing owner-facing standardization with enhanced sponsor reporting, quarterly distribution data, and denominator-oriented surveillance infrastructure. That combination is proportionate: it does not suspend access to the product, but it does impose the minimum auditable controls necessary for CVM to monitor whether the product can continue to be used safely under actual conditions of practice.

(vi) An Updated Veterinarian Communication and a Centralized Public Resource are Necessary to Ensure Uniform Implementation of Safe-Use Conditions (Requested Action E)

Requested Action E is warranted because communication has already occurred, but it has not yet been consolidated into a stable, current, and centrally maintained implementation framework. CVM has issued a Dear Veterinarian Letter, recommended labeling revisions, and recommended a Client Information Sheet. Those measures were important, but the record now shows that serious outcomes continued to accumulate after they were deployed. Once CVM adopts enforceable safe-use conditions, veterinarians and owners will need one authoritative, current source that explains what has changed, how the new conditions operate in practice, and what specific steps should be taken when warning signs emerge.

An updated Dear Veterinarian communication and a dedicated CVM public resource serve that function. They do not substitute for labeling or for enforceable conditions of use; they operationalize them. They also reduce the risk of fragmented or outdated understanding among practitioners, owners, and professional organizations by ensuring that current warnings, stop rules, prescribing prerequisites, and reporting expectations are accessible in one place and updated on a rolling basis as post-market information develops. For a product associated with a persistent and evolving post-market safety signal, this type of centralized implementation support is a practical and proportionate component of the overall safe-use framework.

CVM's December 2024 Dear Veterinarian Letter was issued before the labeling revision was finalized, before the post-SAER signal trajectory was fully apparent, and before the Farrell et al. and Dewey and Brunke studies were published. An updated communication is necessary to:

- Notify practitioners of the continued post-SAER accumulation of adverse events despite the prior communication;
- Communicate whatever prescribing prerequisites, stop rules, and monitoring requirements CVM adopts;
- Clarify the discontinuation triggers and re-dosing prohibitions that the revised labeling should contain;
- Reinforce enhanced reporting expectations; and
- Provide uniform guidance for clinical decision-making when neurologic or musculoskeletal adverse signs occur.

This is a straightforward exercise of CVM's established communication practice and requires no novel authority. It should be issued contemporaneously with any labeling revision to ensure that the new conditions of use are implemented uniformly and without delay.

(vii) Independent Advisory Review Committee Convening Is Warranted by the Severity of the Signal and Required for Consistency with CVM's Own Precedent (Requested Action F)

Requested Action F is warranted because Librela's post-market safety profile now presents exactly the kind of issue for which advisory review is most valuable: a serious, multisystem, post-approval signal; a body of agency pharmacovigilance analysis; independent peer-reviewed corroboration; and a need for public evaluation of what risk-mitigation measures are proportionate going forward. An independent advisory review would not replace CVM's regulatory judgment. It would provide independent external scientific input, create a public transcript and advisory record, and strengthen the administrative basis for whatever action CVM ultimately takes.

CVM convened the Veterinary Medicine Advisory Committee in connection with the ProHeart 6 RiskMAP process twice — on January 31, 2005, before allowing ProHeart 6's return to market, and on March 24, 2010, to evaluate relaxation of RiskMAP restrictions. The ProHeart 6 signal that prompted VMAC convening — anaphylaxis, liver disease, autoimmune hemolytic disease, seizures, and death — is, by every metric available, less severe than the Librela post-market record.

If CVM found the ProHeart 6 record sufficiently serious to warrant VMAC convening, consistency requires the equivalent ad hoc advisory committee convening for Librela. An independent advisory review committee meeting would provide CVM with independent scientific input, create a public record of expert deliberation, and generate an advisory finding that would support comprehensive regulatory action.

Metric	ProHeart 6 (at Recall, 2004)	Librela (Q4 2025)
Total ADE reports	5,913	16,042
Death/euthanasia outcomes	~616	2,712
Death-to-total-report ratio	~10.4%	~16.9%
Disproportionality signals	Not documented via DPA	18 distinct preferred terms
Positive rechallenge cases	Not documented	7 confirmed
Vet suspicion rate	Not reported in this Metric	80% (vs. 32% baseline)

Metric	ProHeart 6 (at Recall, 2004)	Librela (Q4 2025)
Peer-reviewed mechanistic studies	None at time of recall	4 published (Farrell, Dewey/Brunke ×2, von Pfeil)
International regulatory action	None (no foreign regulatory action recorded)	UK VMD SPC update adding musculoskeletal AEs (May 2026)
Communication measures attempted	3 label revisions, 1 CIS, 2 Dear Doctor letters	1 label revision, 1 CIS recommendation, 1 Dear Vet Letter
Signal arrested by communication?	No – prompted recall	No — continued accumulation
CVM's response	Voluntary withdrawal → comprehensive RiskMAP	Communication-based measures only (to date)
Time from launch to CVM action	~3 years (2001–2004)	~3 years (2023–2026) — pending

Sources: Kuehn BM, JAVMA News (Oct. 1, 2004) (Exhibit 17); SAER (Exhibit 1); ProHeart 6/12 RiskMAP (Exhibit 15)

As detailed in Section (vii) above, Dr. Sundlof explained that the same pattern — communication measures failing to arrest a serious signal — prompted CVM's most comprehensive regulatory action. At the time of recall, the FDA had received 5,913 adverse event reports with approximately 616 deaths, after three label revisions, a client information sheet, and two Dear Doctor letters had failed to contain the signal."[270] The Librela record presents a similar pattern — but with substantially greater severity.

If CVM found the ProHeart 6 signal sufficiently serious to warrant a comprehensive Risk Minimization Action Plan including mandatory veterinarian certification, weekly adverse event reporting, and a Client Information Sheet before every administration, then consistency requires equivalent measures for a product whose post-market safety profile is demonstrably more severe across every applicable dimension: absolute adverse event scale (16,042 ADE reports and 2,712 death/euthanasia outcomes for Librela, compared to 5,913 reports and approximately 616 deaths for ProHeart 6 at the time of recall), veterinarian suspicion rate (80% vs. 32% baseline), signal breadth (18 disproportionality signals across multiple organ systems), rechallenge confirmation

[270] JAVMA News

(7 documented positive rechallenge cases), mechanistic coherence, and independent peer-reviewed corroboration.

(viii) The Alternative Request Preserves CVM's Statutory Obligation (Requested Action G)

Petitioner does not urge withdrawal but rather enforceable safe-use conditions described in Requested Actions A through F as the appropriate and proportionate response to the current evidentiary record.

However, it would be inconsistent with the petition's purpose — and with the statute — to request enhanced safe-use conditions without acknowledging the possibility that those controls may prove insufficient. Under 21 U.S.C. § 360b(e)(1)(B), the Secretary shall withdraw approval when "new evidence not contained in such application or not available to the Secretary until after such application was approved . . . evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved."

If CVM determines that no feasible combination of labeling revisions, prescribing prerequisites, owner disclosure requirements, and enhanced monitoring can provide reasonable assurance that bedinvetmab is safe under its labeled conditions of use, then the statutory consequence is clear. The drug would not be "shown to be safe" under its approved conditions of use, and the Secretary's obligation under § 360b(e) would be implicated.

The ProHeart 6 precedent demonstrates both paths. CVM negotiated comprehensive RiskMAP controls as conditions for return to market — and CVM's own assessment is that those controls worked, producing "a decrease in reports of death associated with anaphylactic reactions relative to estimated exposure." But the withdrawal authority remained available as the ultimate enforcement mechanism. Petitioner requests the same graduated framework for Librela: enforceable controls first, with withdrawal authority preserved if those controls prove insufficient.

(ix) The Requested Actions Are Proportionate, Precedented, and Necessary

If CVM found the ProHeart 6 record sufficiently concerning to support a comprehensive RiskMAP, Librela's record compels no less — and is, by every available metric, demonstrably more severe.

The legal authority supporting each requested action is set forth in Section II.B. and rests on the same statutory framework under which CVM implemented the ProHeart 6 and ProHeart 12 RiskMAP.

Every measure requested in this petition has a direct precedent in CVM's own prior regulatory practice:

Requested Action	ProHeart 6/12 RiskMAP Precedent
Post-approval safety studies	ProHeart 6 RiskMAP: enhanced pharmacovigilance with weekly ADE reporting plus mandatory post-approval continuation study commitments as conditions of return to market and semiannual analyses
Prominent labeling revisions with stop rules	ProHeart 6/12: detailed precautions, warnings, and instructions in approved labeling
Prescribing prerequisites	ProHeart 6/12 RiskMAP: mandatory health assessment, veterinarian training and certification before prescribing
Standardized owner-facing risk disclosure	ProHeart 6/12 RiskMAP: mandatory CIS before every administration, documented counseling
Enhanced pharmacovigilance and reporting	ProHeart 6/12 RiskMAP: weekly ADE reports, semiannual summary analyses, CVM-auditable data
Updated Dear Veterinarian communication	ProHeart 6/12 RiskMAP: Dear Doctor letters upon RiskMAP changes
Independent Advisory Review Committee convening	ProHeart 6: VMAC convened January 31, 2005 and March 24, 2010
Withdrawal authority as enforcement backstop	ProHeart 6: voluntary withdrawal in 2004; return to market in 2008 under negotiated RiskMAP

Librela's post-market safety record — by every available metric — is more severe than the ProHeart 6 record that prompted voluntary withdrawal and a comprehensive RiskMAP:

- **Scale**: Petitioner's current Q4 2025 fatal-outcome analysis identifies 3,440 U.S. reports involving 3,481 individual dogs with death/euthanasia fatal outcomes, in addition to the broader adverse-event accumulation documented in CVM and FOIA materials.
- **Veterinarian suspicion:** 80% probable or possible causal attribution, compared to the 32% baseline for all other drugs.
- **Signal breadth:** 18 positive disproportionality signals across multiple organ systems.
- **Rechallenge confirmation:** Seven documented positive rechallenge cases among the 80 cases assessed as probably associated.
- **Mechanistic coherence:** Independent peer-reviewed studies establishing biological plausibility for both the neurological and musculoskeletal signals.

- **Class-wide precedent**: FDA/CDER's tanezumab advisory record documents serious human anti-NGF RPOA and joint-destruction safety concerns relevant to risk-context analysis.

Dr. Stephen Sundlof, then-Director of CVM, explained the rationale for requesting ProHeart 6's voluntary withdrawal: "Despite [our and the company's efforts], we have continued to see a high number of adverse events. The thing that was more troubling for us was that the severity of the events was unchanged or going up. We felt that until we have a better understanding of why we were seeing these severe adverse drug reactions, it was prudent to remove the drug from veterinary use." Dr. Sundlof noted that this was "the first time in his 10 years as director that the center has requested a product recall because of adverse event reports." At the time of recall, the FDA had received 5,913 adverse event reports for ProHeart 6, with approximately 616 deaths. The company had previously made three label revisions, added a client information sheet, and issued two Dear Doctor letters — communication-based measures that had failed to arrest the signal.[271]

***Consistency Obligation*.** CVM is bound by principles of consistent regulatory practice to apply at minimum equivalent measures to a product whose post-market safety profile is demonstrably more severe than the profile that justified the ProHeart 6 recall and RiskMAP.[272] The factual record that prompted CVM's request for ProHeart 6's voluntary withdrawal — 5,913 ADE reports with approximately 616 deaths— is, by every available metric, less severe than the record now documented for Librela.[273]

If CVM's response to the Librela signal is limited to communication-based measures — while the full ProHeart 6 RiskMAP remains in effect as ongoing policy for a product with a less severe safety record — CVM should explain, with specificity, why the more severe Librela signal does not warrant measures at least equivalent to those imposed on the less severe ProHeart 6 signal.[274]

(x) The Serious Consequences of Continued Delay

Every month that Librela is administered without enforceable safe-use conditions, veterinarians prescribe a drug with a documented, persistent, and mechanistically coherent serious adverse event profile — without prospective incidence data, without labeled stop rules, without

[271] *Id*.
[272] See 5 U.S.C. § 706(2)(A); FCC v. Fox Television Stations, Inc., 556 U.S. 502, 515 (2009) (agency departing from prior practice must provide "reasoned explanation" and "display awareness that it is changing position"); see also Judulang v. Holder, 565 U.S. 42, 55 (2011) (agency action treating similar cases differently without rational basis is arbitrary and capricious).
[273] JAVMA News
[274] *See* Motor Vehicle Mfrs. Ass'n v. State Farm Mutual Auto. Ins. Co., 463 U.S. 29, 43 (1983) (agency must "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made") (internal quotation omitted).

standardized owner disclosure, and without the diagnostic baseline necessary to detect progressive harm.

Every month, elderly dogs receive an injection of a drug whose biological activity persists for weeks following administration, with no pharmacological reversal agent available if adverse events emerge. The mechanism of action suppresses a neurotrophic factor essential for the survival of the neurons most vulnerable to age-related degeneration — and their owners are not systematically informed of what CVM's own pharmacovigilance analysis has found.

Every month, the denominator grows and the numerator grows with it — and the data necessary to distinguish drug-caused harm from background disease progression remain uncollected because the prospective studies necessary to generate that data have not been required.

CVM's own communication-based interventions — the Dear Veterinarian Letter, the Post-Approval Experience labeling section, the recommended Client Information Sheet — have not arrested the signal's accumulation. This is the precise circumstance in which the RiskMAP framework was designed to operate: when a drug with documented serious adverse events requires controls that go beyond what voluntary communication can achieve.

The statutory framework places an affirmative, continuous obligation on both the sponsor and the Agency to ensure that an approved new animal drug remains safe under its labeled conditions of use. 21 U.S.C. § 360b(a)(1)(A). CVM's own pharmacovigilance findings, corroborated by independent peer-reviewed analysis and grounded in the known pharmacology of the drug, establish that the current conditions of use — labeling, monitoring, and risk communication — are not sufficient to maintain that standard.

The actions requested in this petition — prospective safety studies, enhanced labeling with stop rules, prescribing prerequisites, standardized risk disclosure, and updated practitioner communication — are the minimum measures necessary to:

(a) Generate the denominator-based safety data that the pre-approval program did not produce and that the spontaneous reporting system cannot provide;

(b) Operationalize enforceable conditions of use that the post-approval record now demands;

(c) Ensure that veterinarians have the clinical guidance necessary to prescribe safely and to recognize and respond to adverse events;

(d) Ensure that pet owners have the information necessary to make informed treatment decisions about a drug with serious, persistent, and irreversible risks; and

(e) Establish the pharmacovigilance infrastructure necessary for CVM to determine, on an ongoing basis, whether the drug continues to meet the statutory safety standard.

These are not burdensome or unprecedented measures. They are measures that CVM itself has previously implemented — and found effective — for an approved animal drug with a less severe safety record. They are proportionate to the documented severity of the safety signal. They are consistent with the statutory and regulatory authorities identified in Section II.B. And they are necessary to protect the health and welfare of the companion animals whose owners trust that an FDA-approved product has been determined to be safe under its labeled conditions of use — a trust that the current evidentiary record calls into serious question.

(xi) Conclusion

The evidentiary record before CVM — comprising the Agency's own authoritative pharmacovigilance analysis, independent peer-reviewed studies by board-certified veterinary specialists, the known pharmacology of sustained NGF suppression in aging animals, the directly analogous human anti-NGF clinical experience, and the international post-market record — warrants the grant of each requested action.

Taken together, Requested Actions A through F form a progressive, internally coherent safe-use framework responsive to the deficiencies now documented in Librela's post-approval record. Requested Action A generates the prospective evidence the approval record lacks. Requested Action B corrects the immediate inadequacy of the current label. Requested Action C operationalizes those warnings at the point of care. Requested Action D ensures that owners receive standardized risk information and that CVM obtains the enhanced reporting necessary for ongoing oversight. Requested Action E provides the implementation layer. Requested Action F strengthens the scientific review and administrative record supporting CVM's response. These measures preserve access for appropriately selected patients while conditioning that access on the safeguards now necessary to satisfy the statutory safety standard.

The significance of this record extends beyond Librela. Under 21 U.S.C. § 360b(d)(2)(B), FDA must consider the cumulative effect of a drug and any pharmacologically related substance in evaluating the safety of new applications. The post-market experience with bedinvetmab, the human anti-NGF clinical record, and the published mechanistic literature collectively constitute information directly pertinent to the § 360b(d) safety evaluation of any pending or future anti-NGF application. Petitioner respectfully submits that CVM should fully address the unresolved safety questions identified herein — through the post-approval studies and enhanced pharmacovigilance requested — before concluding that any pharmacologically related product satisfies the statutory safety standard.

Petitioner urges CVM to act – not to punish, not to relitigate, but to protect – with the urgency that the ongoing accumulation of serious, irreversible, and in too many cases fatal adverse events demand.

III. Environmental Impact Statement

The undersigned claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have a significant effect on the human environment.

IV. Economic Impact Statement

An Economic Impact Statement may be provided upon request.

V. Appendices

The following exhibits are attached to and incorporated by reference in this Petition:

- **Exhibit 1**: FDA, Center for Veterinary Medicine, Standard Adverse Event Review, Librela (bedinvetmab injection), NADA 141-562, DPS-2024-141 (September 10, 2024)

- **Exhibit 2**: FDA, Center for Veterinary Medicine, Dear Veterinarian Letter Notifying Veterinarians About Adverse Events Reported in Dogs Treated with Librela (December 16, 2024)

- **Exhibit 3**: FDA, Center for Veterinary Medicine, Untitled Letter to Zoetis Inc. re: NADA 141-562, Misleading Efficacy Claims, CMS # 665089 (November 20, 2023)

- **Exhibit 4**: FDA, Center for Veterinary Medicine, Untitled Letter to Zoetis Inc. re: NADAs 141-562, 141-546, 141-502, False and Misleading Advertising, CMS # 691206 (February 5, 2025)

- **Exhibit 5**: Farrell M, et al. Musculoskeletal adverse events in dogs receiving bedinvetmab (Librela). *Frontiers in Veterinary Science*, May 2025 (published May 9, 2025)

- **Exhibit 6**: Dewey CW, Brunke MW. Commentary: Musculoskeletal adverse events in dogs receiving bedinvetmab (Librela). *Frontiers in Veterinary Science*, July 2025 (published July 16, 2025)

- **Exhibit 7**: Dewey CW, Brunke MW. Dysmetabolism of the nerve growth factor pathway in the aging brain plays a pivotal role in cognitive decline. *J Am Vet Med Assoc*. 2026;264(4):471–475. doi:10.2460/javma.25.09.0578 (published online December 5, 2025)

- **Exhibit 8**: FDA, Center for Veterinary Medicine, Freedom of Information Summary, NADA 141-562, Librela (bedinvetmab injection), and associated approval/study summary materials

- **Exhibit 9(a)**: Librela (bedinvetmab injection) U.S. Prescribing Information, Original (Approved May 5, 2023)

- **Exhibit 9(b)**: Librela (bedinvetmab injection) U.S. Prescribing Information, Revised (January 2025)

- **Exhibit 9(c):** Librela (bedinvetmab injection) Client Information Sheet

- **Exhibit 10(a):** European Medicines Agency ("EMA") European Public Assessment Report ("EPAR") materials relating to bedinvetmab (Librela), submitted solely for comparative international regulatory-context purposes

- **Exhibit 10(b):** Zoetis Canada Inc., LIBRELA (bedinvetmab injection) Canadian Package Insert, DIN 02511797 et al. (October 17, 2022), submitted solely for comparative international regulatory-context purposes.

- **Exhibit 10(c):** Zoetis Canada Inc., LIBRELA (bedinvetmab injection) Canadian Product Monograph, DIN 02511797 et al. (revised June 27, 2024)

- **Exhibit 10(d):** Zoetis Inc., Draft Product Labels, LIBRELA (bedinvetmab injection), Canadian Regulatory Submission Package Insert Mock-Up, Zoetis Version (January 28, 2021)

- **Exhibit 11(a)** : FDA/CDER Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Tanezumab Advisory Materials, Briefing Document (March 24-25, 2021)

- **Exhibit 11(b):** FDA/CDER Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Tanezumab Advisory Materials, Transcript (March 25, 2021)

- **Exhibit 12**: Berenbaum F, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. Annals of the Rheumatic Diseases, 2020;79:800-810 (full article)

- **Exhibit 13(a):** Methodology for Petitioner's Analysis of CVM Adverse Event Data for Librela (Q4 2025);

- **Exhibit 13(b):** Petitioner's Analysis of CVM Adverse Event Data for Librela (Q4 2025), including Figure 13-1: Librela Death/Euthanasia Fatal Outcomes by Quarter (All Cases); Figure 13-2: Librela Death/Euthanasia Fatal Outcomes by Quarter (Monotherapy Cases); Figure 13-3: Fatal-Outcome Time-to-Onset Distribution (All Cases); Figure 13-4: Fatal-Outcome Time-to-Onset Distribution (Monotherapy Cases); supporting summary values; AER methods note; and traceability references to the current Q4 2025 chart/output files. Source: U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) Adverse Event Reporting System (public quarterly JSON files). Analysis and visualization by Jeffrey Gibson, Independent Researcher & Data Analyst, 2026.

- **Exhibit 14(a):** FDA, Center for Veterinary Medicine, Response to FOIA Request re: Librela ADE Reports, May 5, 2023, through June 30, 2025 (ADE database search performed July 16, 2025)

- **Exhibit 14(b)**: FDA, Center for Veterinary Medicine, Response to FOIA Request re: ADE Database Records for Librela, NADA 141-562, Reports Received May 5, 2023, through Sept. 30, 2025 (ADE database search performed Oct. 27, 2025)

- **Exhibit 14(c):** FDA, Center for Veterinary Medicine, Response to FOIA Request re: ADE Database Records for Librela, Reports Received May 5, 2023, through Dec. 31, 2025 (ADE database search performed Jan. 22, 2026)

- **Exhibit 14(d):** FDA, Center for Veterinary Medicine, Response to FOIA Request re: ADE Database Records for Librela, Reports Received May 5, 2023, through June 30, 2024 (ADE database search performed July 11, 2024)

- **Exhibit 15**: Risk Minimization Action Plan (RiskMAP) for ProHeart® 6 (moxidectin) for Extended-Release Injectable Suspension, NADA 141-189, and ProHeart® 12 (moxidectin) for Extended-Release Injectable Suspension, NADA 141-519 (July 2, 2019)

- **Exhibit 16**: Reauthorization of the Animal Drug User Fee Programs: Hearing Before the Subcommittee on Health of the House Committee on Energy and Commerce, 118th Congress (March 30, 2023). Written Statement of Tracey Forfa, J.D., Director, FDA Center for Veterinary Medicine, and relevant oral testimony excerpts.

- **Exhibit 17**: Kuehn BM, "Fort Dodge recalls ProHeart 6, citing FDA safety concerns," JAVMA News, Oct. 1, 2004.

- **Exhibit 18**: UK Veterinary Medicines Directorate, Summary of Product Characteristics: Librela Solution for Injection for Dogs, Vm 42058/5033, AN: 00241/2026 (approved May 20, 2026)

- **Exhibit 19**: Von Pfeil DJF, Armitage A, Nelson NC. Emerging Signs of Rapidly Progressive Arthritic Changes in Dogs and Cats Receiving Bedinvetmab and Frunevetmab. *Vet Comp Orthop Traumatol* 2026;39:157–161. doi: 10.1055/a-2846-8347 (published May 12, 2026)

VI. Certification

The undersigned certifies that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition, in compliance with 21 C.F.R. § 10.30(b).

Acknowledgment: Petitioner gratefully acknowledges the analytical contributions of **Jeffrey Gibson**, independent researcher and data analyst who developed the methodology described in Exhibit 13(a).and conducted the analysis of CVM's publicly available adverse event data presented in Figures 13-1 through 13-4 and set forth in Exhibit 13(b).

Respectfully submitted,

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