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Introduction

The Center for Veterinary Medicine (CVM) has the regulatory responsibility for ensuring the safety of marketed animal drug products. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness under the labeled conditions of use. Many of the common adverse events may become known prior to approval. CVM maintains a post-approval monitoring system to detect adverse events that occur after the new animal drug is approved. After approval, the drug will be used in a larger and more diverse population.

This document describes CVM's method for evaluating adverse drug experience reports associated with animal drugs and provides data on adverse drug events reported for canine heartworm preventives. It demonstrates that the number of reports of serious adverse drug events, such as anaphylaxis, convulsions, liver abnormalities, immune-mediated hemolytic anemia, thrombocytopenia, and death, is substantially higher for ProHeart 6 (moxidectin sustained release) than for other heartworm preventives. The frequency of ProHeart 6 adverse drug event reports, the severity of the clinical manifestations within the reports, and the temporal association with drug administration raise serious questions about the safety of this heartworm prevention product. Fort Dodge, at FDA's request, agreed to immediately cease production and recall Proheart 6 from the market until the safety concerns associated with the product are resolved.

Definitions

Adverse drug experience (ADE): Any adverse event associated with the use of a new animal drug, whether or not considered to be drug related and whether or not the new animal drug was used in accordance with the approved labeling (CFR 514.3.doc).[1] Adverse drug experience includes, but is not limited to:

(1) An adverse event occurring in animals in the course of the use of an animal drug product by a veterinarian or by a livestock producer or other animal owner or caretaker.

(2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).

(3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of a new animal drug.

In this document the term "adverse drug event" is used interchangeably with "adverse drug experience.

Serious adverse drug experience: An adverse event that is fatal, or life threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement.

Unexpected adverse drug experience: An adverse event that is not listed in the current labeling for the new drug and includes any event that may be symptomatically and pathophysiologically related to an event listed on the labeling, but differs from the event because of greater severity of specificity.

ADE report: An adverse drug experience report submitted by a sponsor on Form 1932 or by a veterinarian or consumer on Form 1932a. [2, 11] Nearly all of the reports submitted to CVM by drug sponsors are identified with a unique sponsor case number.

Correspondence date: The date an ADE report is postmarked.

Clinical manifestation: Equivalent to a clinical sign or outcome and can be a primary, secondary, or tertiary clinical sign or outcome. A report may contain several clinical manifestations.

Causality assessment: The evaluation and scoring of a clinical manifestation using the modified Kramer algorithm. There is a causality assessment score for every clinical manifestation in a report. Causality assessment scores are grouped into causality assessment categories:

Causality Assessment Scores	Causality Assessment Categories
-9	Not applicable
-8	Information lacking
-7	No conclusion
-1 to -6	Remotely drug-related
0 to 2	Possibly drug-related
3 to 5	Probably drug-related
6 to 7	Definitely drug-related

If clinical manifestations in an ADE report cannot be attributed to a single animal, an assessment could involve more than one animal. For companion animals, there is usually one animal for each assessment.

Episode: The occurrence of one or more clinical manifestations in the smallest number of animals to which the clinical manifestation(s) can be uniquely ascribed. If clinical manifestations in an ADE report cannot be attributed to a single animal, an episode could include more than one animal. For companion animals, there is usually one animal in each episode.

Time of onset: The duration of time between drug administration and onset or detection of a clinical manifestation.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (World Health Organization). [27]

Adverse Event Reporting for Animal Drugs

In the United States, the Center for Veterinary Medicine (CVM) approves new animal drugs under Section 512 of the Federal Food, Drug, and Cosmetic Act based on applications that include full reports of investigations which have been made to show whether or not the drug is safe and effective for use. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness. Thus, most of the common adverse events will become known during those pre-approval studies. Post

approval monitoring of adverse drug events is a widely accepted method for monitoring the safety and effectiveness of approved drugs when used in a larger, heterogeneous population.[21] Goals of CVM's pharmacovigilance program include: (1) providing pertinent safety information for the product label, (2) monitoring for unsafe or defective products, and (3) monitoring for unsafe drug-use practices.[4]

Post approval monitoring is critical to ensuring that drugs approved as safe and effective continue to be so; however, it has some inherent limitations. In the United States, reporting of adverse drug events by physicians and veterinarians is entirely voluntary and accomplished through passive reporting systems. It is well recognized that adverse drug events are substantially under-reported.[5, 6, 7, 8, 9, 10, 21] When an adverse drug event is reported, accurate assessment of the event depends upon the general quality and completeness of the report. Additional limitations in veterinary pharmacovigilance include the cost and availability of diagnostic tests and the lack of comprehensive post-mortem information. Veterinary clinical care is becoming more sophisticated, and reports currently submitted to CVM are more comprehensive than 10 years ago.[20]

In most cases, national ADE reporting rates can only be estimated because the population at risk (number of patients exposed to a particular product) is not precisely known. Furthermore, an ADE reporting rate is **not** an incidence rate because ADEs are substantially under-reported (numerator) and accurate data on the number of exposed patients (denominator) is often lacking.[28] A reporting rate that is high compared to the background incidence rate may signal a problem with a product. However, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily mean that the product in not associated with an increased risk of an adverse event.

CVM currently receives about 25,000 adverse drug experience reports per year. Approximately 99% of ADE reports are received from drug sponsors. A sponsor of a new animal drug completes Form 1932 when it receives a report (by telephone, mail or e-mail) of an adverse event from a veterinarian or a consumer. Under the mandatory reporting requirement of CFR 21§514.80 (and formerly under CFR 21§510.300), sponsors are required to submit a Form 1932 to FDA within 15 working days for each serious, unexpected ADE. Under CFR 21§514.80, sponsors must report other ADEs in

periodic Drug Experience Reports, which are submitted every 6 months for the first 2 years following product approval and yearly thereafter. Approximately 1% of ADE reports come directly to CVM from pet owners and veterinarians on Form 1932a. Each ADE report contains one or more clinical manifestations, which are coded by CVM according to a standard dictionary of clinical terms.[12]

When an ADE report arrives at CVM, it is logged into the Document Control Unit, assigned a submission number, and forwarded to the Division of Surveillance for processing. CVM safety reviewers, who are experienced clinical veterinarians, then review the individual ADE reports. The safety reviewers enter all relevant information such as age, breed, history, pre-existing problems, and concomitant drugs into an Oracle database called the Submission Tracking and Reporting System (STARS).

The reviewers evaluate each clinical manifestation reported using a scoring system that has been previously described.[3, 4, 13] This system is a modified version of the Kramer algorithm, a human adverse drug event algorithm.[14, 25, 26] This scoring system has the following 6 components:

1. **Previous Experience with the Drug**
2. **Alternative Etiologic Candidates**
3. **Timing of Events**
4. **Evidence of Overdose**
5. **Dechallenge** (whether the problem disappears after withdrawal of the drug)
6. **Rechallenge** (whether the problem reappears when the drug is reintroduced)

Consideration is given to information about age, breed, gender, pre-existing conditions, and concomitant drugs. A summary causality assessment score for each clinical manifestation is determined and entered into the STARS database. The summary score corresponds to the strength of the association between the drug and the clinical manifestation and ranges between -9 and +7. Clinical manifestations with summary scores of ≥0 are considered possibly, probably, or definitely drug-related. When many ADE reports listing a particular clinical manifestation have accrued for a particular drug, CVM assigns a higher "previous experience" component score for that clinical manifestation in subsequent ADE reports. Therefore, scores for a particular

manifestation may increase over time. Dechallenge and rechallenge components of Kramer score usually don't apply with a sustained release product like ProHeart 6 so the maximum causality assessment score for such products is usually +4 unless there is an overdose, in which case it can be +5. Detailed information about the components of the algorithm used by CVM may be found in Appendix A. Causality assessment scores for ineffectiveness can be as high as +6 because CVM uses a modified version of this algorithm for ineffectiveness complaints. [29]

Follow-up reports are an important part of pharmacovigilance. 21 CFR 514.80(b)(2)(ii). They generally arrive within a month or two after the initial report. A new record is not created for follow-up reports; the information in a follow-up report is added to that in the initial report. In some cases, there may be more than 3 follow-up reports per original ADE report. Follow-up reports provide significant new information that may either strengthen or weaken the association between an event and use of the drug. In addition, follow-up reports may provide new clinical manifestations or outcomes to previously reported ones. For example, in the absence of a follow-up report, a severe outcome such as death may go unreported.

The severity and frequency of clinical manifestations in the STARS database are continuously monitored by CVM. STARS data summaries may be generated by cumulative experience or by detailed search criteria such as age, time of onset, attending veterinarian opinion, gender, and breed. The cumulative numbers of dogs with reported clinical manifestations that had causality assessment scores of zero or above are placed in the public domain on the CVM website by active ingredient and route of administration.

When severity or frequency of reported ADEs for a given product are of concern, the Division of Surveillance may request additional information from the drug sponsor or organize an internal CVM product safety meeting to review available data. At the product safety meeting, CVM determines whether a label revision or any other action is indicated.

Canine Heartworm Disease

Heartworm disease is a serious but preventable mosquito-borne parasitic disease that primarily affects dogs and cats. It is caused by the *Dirofilaria immitis* nematode. Dogs are usually asymptomatic until maturation of heartworm larvae in the right atrium

and pulmonary artery causes cardiopulmonary effects. Typically, maturation of the larvae takes about six months. The chances of contracting heartworm disease without prophylaxis depend on exposure to mosquitos. Dogs are more likely to become infected if they live in the Southeast, Gulf Coast, or Mississippi River Valley near fresh or saltwater, are housed outside, and are not receiving heartworm preventives. Dogs can survive a heartworm infection by receiving appropriate treatment. There is a risk of thromboembolism and death following adult heartworm treatment when worms break loose from their location in the right heart, and there can be side effects from the drugs that are commonly used to treat adult heartworms. Additional information about canine heartworm disease can be found through the American Heartworm Society. [30, 31]

Macrocyclic Lactones

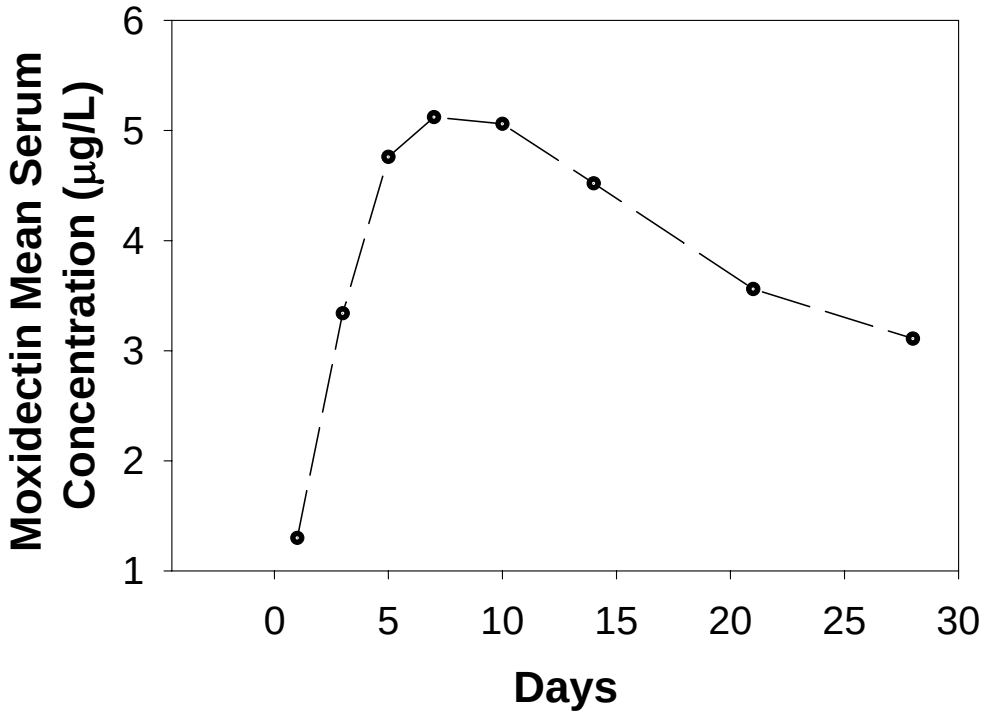
The macrocyclic lactones are natural fermentation products of soil-dwelling bacteria of the genus *Streptomyces*. They have activity against both internal and external parasites, specifically nematodes (including heartworms) and arthropods. Macrocyclic lactones consist of two major groups, the avermectins and the milbemycins. Moxidectin is a member of the milbemycin group. The other macrocyclic lactones approved for use in dogs include ivermectin, milbemycin oxime, and selamectin. [32] Known signs of macrocyclic lactone toxicity in mammals include dilated pupils, vomiting, diarrhea, salivation, disorientation, lack of coordination, muscle twitching, tremors, depression, coma, and blindness. Severe reactions can involve other neurologic signs such as seizures which have been added to the post-approval safety information on several macrocyclic lactone labels. [32]

ProHeart 6 Product Information

ProHeart 6 is a sustained release microencapsulated preparation of moxidectin. It is indicated for use in dogs at least 6 months of age and older as a 6-month heartworm preventive. It is also approved for treatment of existing larval and adult hookworm infections in dogs. It is manufactured and sold by Fort Dodge Animal Health (FDAH), the veterinary division of Wyeth Pharmaceuticals, under the new animal drug application (NADA) number 141-189. ProHeart 6 is sold in multi-dose vials. The Freedom of Information Summary describes conditions of approval for this product. [15] A copy of the

current label for ProHeart 6 can be found in Appendix C. [16] ProHeart 6 is the only heartworm prevention product that is approved in the U.S. for parenteral administration in dogs; it is administered subcutaneously (under the skin). Following injection, mean ProHeart 6 blood levels peak 7-14 days post-administration. Figure 1 shows mean moxidectin serum levels following a single injection of ProHeart 6. [15]

Figure 1. Mean serum moxidectin concentrations following a single injection of ProHeart 6 in dogs



The other major canine heartworm preventives (ivermectin, milbemycin, and selamectin) are delivered as a monthly dose; ivermectin and milbemycin are administered orally and selamectin is administered topically. ProHeart, a once-a-month moxidectin tablet, is also manufactured and sold by FDAH, but is not commonly used in dogs in the United States. A listing of approved monthly and 6-month heartworm prevention products and their indications can be found in Appendix B.

Regulatory History of ProHeart 6

ProHeart 6 was approved under NADA 141-189 on June 6, 2001 based on pre-approval safety and effectiveness studies. Laboratory studies revealed no serious adverse drug events in healthy dogs. In clinical field studies, the following adverse reactions were reported in approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and increased body temperature. The death of 3 dogs (2 geriatric dogs and 1 dog with a history of health problems) resulted in the following **PRECAUTION** statement on the label: **Use with caution in sick, debilitated or underweight animals**.

Since approval of ProHeart 6, three label revisions have been initiated by the Division of Surveillance at CVM because of serious and unexpected adverse drug reactions. The first label revision, which was approved on June 13, 2002, added the post-approval reported clinical manifestations of anaphylaxis/anaphylactoid reactions, depression/lethargy, urticaria, and head/facial edema. The second revision, which was approved on November 5, 2002, added post-approval reported cardiopulmonary signs associated with administration of the product in heartworm positive dogs. The third revision, which was approved on July 15, 2003, added a Client Information Sheet (CIS) and the phrase "and rare reports of death" to the post-approval adverse reactions section of the label. Two "Dear Doctor" letters describing the label revisions were disseminated by the sponsor to veterinarians. The first letter described the anaphylaxis/anaphylactoid reaction experiences reported and a precaution to test dogs for heartworms before administration. The second "Dear Doctor" letter contained a combined description of the second and third CVM initiated label changes. The current label for ProHeart 6 can be found in Appendix C.

After a clinical manifestation is added to the Adverse Reactions section of the product label, CVM safety reviewers may assign a higher value for the "previous experience" component of a causality assessment score. CVM did not re-evaluate ProHeart 6 ADE reports that were reviewed prior to label changes, but if CVM had re-evaluated them, the causality assessment scores would increase for clinical manifestations added to the product label.

On several occasions, CVM discussed with the sponsor discrepancies in reported adverse drug events and the lack of adequate follow-up information contained in the ProHeart 6 ADE reports, generally through teleconferences. [22, 23, 24,] CVM met with FDAH on January 14, 2004, July, 13, 2004 and September 1, 2004 to discuss the Center's concerns about the frequency and severity of reported ADEs associated with Proheart 6. In addition to safety issues, concerns with the current Good Manufacturing Practices (GMPs) have been noted. In December 2003 FDA issued a **Warning Letter** to FDAH for violations occurring in the ProHeart 6 manufacturing facility. [17] An August 2004 inspection found that the GMP violations had been corrected. Two firm-initiated nation-wide recalls of ProHeart 6 have been made due to GMP problems. The first recall occurred on **April 27, 2004** for failure to meet the 6-month dissolution time point. [18] The second recall was issued on **May 13, 2004** because of failure to meet GMPs and concerns about proper sterilization. [19] An August 2004 inspection found the GMP violations had been corrected.

ADE Reports for ProHeart 6 and Other Heartworm Preventives

This section summarizes STARS searches conducted by CVM for ADEs reported for marketed monthly and 6-month heartworm preventives with the active ingredients: ivermectin, milbemycin, selamectin, and moxidectin. Searches were conducted using correspondence dates for 2 time periods: 1) product approval to September 1, 2004 and 2) June 1, 2001 to September 1, 2004. Only ADEs (including death) considered to be possibly, probably, or definitely related to the products are reported.

Table 1 indicates the number of dogs with reported ADEs for monthly and 6-month heartworm preventives and Table 2 shows the number of deaths among the dogs. Table 1 and Table 2 include all ADEs and deaths (possibly, probably, or definitely drug-related), including those related to "ineffect" for heartworms, hookworms, roundworms, fleas, ticks, and mites.

Table 1. Number of dogs with reported ADEs* that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives.

Heartworm Preventive	Year of Initial Approval	Number of Dogs, Approval to September 1, 2004	Number of Dogs, June 1, 2001 to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	5667	4646
Milbemycin and Milbemycin/Lufenuron	1990	3243	2273
Selamectin	1999	9719	7681
Moxidectin Tablets (ProHeart)	1997	12	1
Moxidectin Sustained Release (ProHeart 6)	2001	5659	5659

*including "ineffect" for heartworms, hookworms, roundworms, fleas, ticks, and mites

Table 2. Number of reported dog deaths that are possibly, probably, or definitely related to marketed monthly or 6-month heartworm preventives.

Heartworm Preventive	Year of Initial Approval	Number of Deaths, Approval to September 1, 2004	Number of Deaths, June 1, 2001 to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	133	50
Milbemycin and Milbemycin/Lufenuron	1990	131	59
Selamectin	1999	171	110
Moxidectin Tablets (ProHeart)	1997	0	0
Moxidectin Sustained Release (ProHeart 6)	2001	485	485

Selamectin had the highest number of dogs with ADE reports. Many of these dogs had reports of ineffect for fleas, mites, and ticks and many had mild local reactions or hair loss at the application site. Between 2001 and 2002, CVM worked with the sponsor of the selamectin product to address serious ADEs that were observed in underweight and debilitated animals. CVM collaborated with the sponsor to add a warning on the label: "Do not use in sick, debilitated or underweight animals" and to develop an in-clinic approach to educating prescribing veterinarians and staff members. The reported safety-related ADEs decreased in frequency and severity. Between 2002 and 2004 the sponsor was also asked to conduct post-approval studies to address reports of ineffectiveness with respect to heartworm prevention. In July 2004, the sponsor issued a Dear Doctor Letter to veterinarians about these studies.

During the period of June 1, 2001 and September 1, 2004, there were more than twice as many deaths reported among dogs that received ProHeart 6 than for all other heartworm preventives combined, even though ProHeart 6 sales represent 21-24% of the market (as reported by FDAH to CVM in January and September, 2004).

Ineffectiveness complaints for heartworm prevention claims were reported for all marketed products including ProHeart 6. CVM discussed this issue at a recent national meeting. [29] Table 3 shows the number dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of marketed monthly or 6-month heartworm preventives. Table 3 also illustrates the small number of deaths that are possibly, probably, or definitely drug-related among those dogs.

Table 3. Number of dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of marketed monthly or 6-month heartworm preventives and the number of reported deaths possibly, probably, or definitely drug-related among those dogs.

Heartworm Preventive	Year of Initial Approval	Number of Dogs, Approval to September 1, 2004	Number of Deaths, Approval to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	906	4
Milbemycin and Milbemycin/Lufenuron	1990	1610	0
Selamectin	1999	2815	11
Moxidectin Tablets (ProHeart)	1997	2	0
Moxidectin Sustained Release (ProHeart 6)	2001	411	4

Table 4 and Table 5 show the number of causality assessments for serious clinical manifestations reported among dogs administered monthly or 6-month heartworm preventives from product approval to September 1, 2004 and from June 1, 2001 to September 1, 2004, respectively. The number of assessments for anaphylaxis/anaphylactoid reactions, convulsions, liver lesions, elevations in SGPT/ALT (serum glutamic-pyruvic transaminase/alanine transferase), low platelets

(thrombocytopenia), and immune-mediated hemolytic anemia (IMHA) were considerably higher for ProHeart 6 than for other heartworm preventives. The number of convulsions in dogs receiving selemectin was high between 2001 and 2002 but has been declining since the warning not to use this product in sick, debilitated or underweight animals was placed on the label in 2002. The numbers of hematologic and liver signs also decreased for selamectin.

Table 4. Number of causality assessments for certain reported clinical manifestations that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives, from approval to September 1, 2004.

Heartworm Preventive (year of initial approval)	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT Elevations	Liver Lesions	Low Platelets	IMHA
Ivermectin and Ivermectin/Pyrantel (all products) (1987)	16	131	38	9	10	20
Milbemycin and Milbemycin/Lufenuron (1990)	36	194	38	8	26	16
Selamectin (1999)	45	304	69	13	50	15
Moxidectin Tablets (Proheart) (1997)	0	1	0	0	0	0
Moxidectin Sustained Release (ProHeart 6) (2001)	1820	378	192	65	124	67

Table 5. Number of causality assessments for certain reported clinical manifestations that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives, June 1, 2001 to September 1, 2004.

Heartworm Preventive	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT elevations	Liver lesions	Low Platelets	IMHA
Ivermectin and Ivermectin/Pyrantel (all products)	13	69	10	2	5	8
Milbemycin and Milbemycin/Lufenuron	20	107	26	5	10	9
Selamectin	37	234	45	8	30	8
Moxidectin Tablets (ProHeart)	0	0	0	0	0	0
Moxidectin Sustained Release (ProHeart 6)	1820	378	192	65	124	67

ProHeart 6 ADEs

Between June 6, 2001 and September 1, 2004, ProHeart 6 ADEs were reported for 6015 dogs (all causality assessment categories). There were 21,885 causality assessments conducted for clinical manifestations reported among these dogs.

Table 6 shows the number of assessments by causality assessment category. There were 19,676 assessments for clinical manifestations determined by CVM to be possibly, probably, or definitely related to the administration of ProHeart 6 (Table 6). These assessments were for clinical manifestations in 5659 dogs (Table 1).

There were 637 dog deaths (all causality assessment categories) reported on ProHeart 6 ADE reports and 485 deaths were determined by CVM to be possibly or probably related to ProHeart 6 (Table 2).

Table 6. **Number of causality assessments for clinical manifestations reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.**

Causality Assessment Category	Number of Assessments
Definitely drug-related	32*
Probably drug-related	4310
Possibly drug-related	15334
Remotely drug-related	2026
Information Lacking	183
Total	**21885**

*clinical manifestations that were considered definitely drug-related all had causality assessment scores of +6 for heartworm ineffect

Among dogs with clinical manifestations that were possibly, probably, or definitely related to the administration of ProHeart 6, 2585 had concomitant drugs and/or vaccines and 2034 did not have concomitant vaccines or drugs. The concomitant drug/vaccine status for the remainder of the dogs is not known. There were 5548 episodes for the 5659 dogs with clinical manifestations that were possibly, probably, or definitely drug-related. The health status of these dogs was noted by the reporting veterinarian as good in 4916 episodes, fair in 544 episodes, and poor in 52 episodes. The health status of dogs in 36 episodes was not reported.

Time of onset refers to the duration of time between drug administration and onset or detection of a clinical manifestation. Table 7 shows the number of causality assessments by time of onset and concomitant drug/vaccine status for clinical manifestations that were determined to be possibly, probably, or definitely related to ProHeart 6 administration.

Table 7. Number of causality assessments by time of onset* and concomitant drug/vaccine status for reported clinical manifestations that are possibly, probably or definitely related to the use of ProHeart 6, June 6, 2001 to September 1, 2004.

Time of Onset	Total Causality Assessments†	Assessments with Concomitant Drugs and/or Vaccines	Assessments without Concomitant Drugs or Vaccines
<3 hours	6613 (34.9%)	2710 (27.5%)	3043 (48.2%)
3 to < 24 hours	2546 (13.4%)	1291 (13.1%)	877 (13.9%)
1 to <3 days	2296 (12.1%)	1279 (13.0%)	660 (10.4%)
3 to <7 days	2178 (11.5%)	1399 (14.2%)	515 (8.2%)
7 to <14 days	1962 (10.4%)	1301 (12.2%)	370 (5.9%)
14 to <30 days	1395 (7.4%)	839 (8.5%)	332 (5.3%)
1 to <3 months	1291 (6.8%)	715 (7.3%)	354 (5.6%)
≥3 months	658 (3.5%)	322 (3.3%)	165 (2.6%)
Total*	**18939**	**9856**	**6316**

***For those with known time of onset

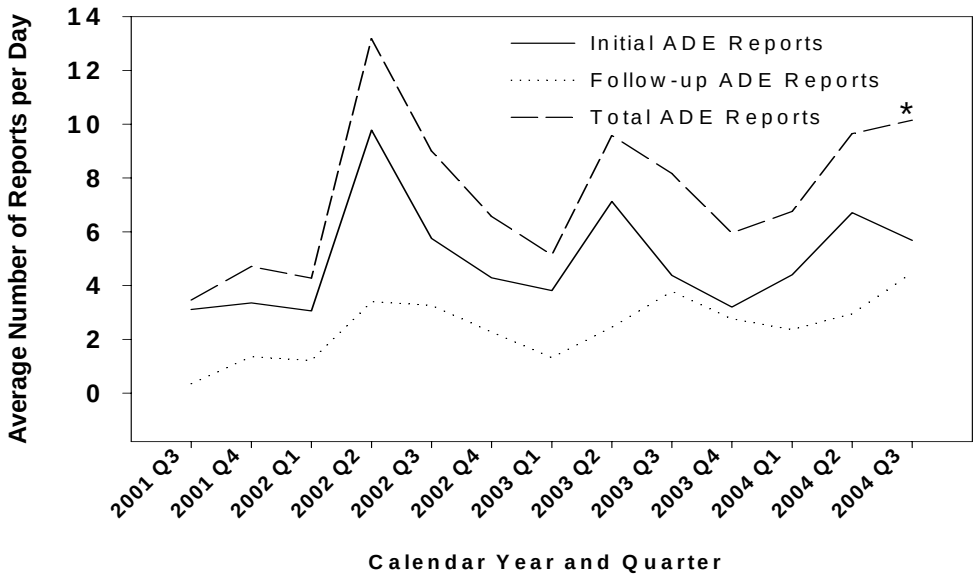
† Includes causality assessments for dogs that had concomitant drugs and/or vaccines, dogs that did not have concomitant drugs or vaccines, and dogs with unknown concomitant drug/vaccine status

The majority of clinical manifestations occurred between 0 and 14 days, when there were rising or peak serum moxidectin levels. Some dogs had no adverse events on initial dosing but did after subsequent doses. CVM encouraged the sponsor to investigate whether the drug could be causing hypersensitivity reactions. Hypersensitivity reactions occur when there is an exaggerated immune response to a foreign substance. Anaphylaxis is one type of hypersensitivity reaction. Preliminary results from studies investigating the possible association between ProHeart 6 and hypersensitivity reactions were discussed at a meeting on January 14, 2004. FDAH postulated that reactions might be due to direct mast cell degranulation.

Trends in ProHeart 6 ADE Reporting

CVM tracks the number of incoming original and follow-up ADE reports as well as severity of reported ADE's. Often, severe ADE's will have follow-up reports. Figure 2 shows the mean number of initial and follow-up ProHeart 6 ADE reports received per day at CVM by calendar quarter (90 to 92 day quarter). Data for the third quarter of 2004 represents the mean number of ADE reports per day across the first 62 days of the quarter. The reporting pattern has remained similar each year, with a peak in the second quarter, coinciding with start of heartworm prevention season (Figure 2).

Figure 2. Mean number of initial and follow-up ProHeart 6 reports received by CVM day, by calendar quarter*.



*Data for the third quarter of 2004 represents the mean number of reports per day across the first 62 days of the quarter

The annual reporting period for a product is based on its approval date, not the calendar year. Table 8 shows the annual number of initial and follow-up ProHeart 6 ADE reports received by CVM from July 1, 2001 to June 30, 2004. The table shows that the annual number of initial ProHeart 6 ADE reports has not decreased over time.

Table 8. Number of ProHeart 6 ADE reports received by CVM, by year (July 1, 2001 to June 30, 2004).

Period	Initial reports	Follow-up reports	Total reports
July 1, 2001-June 30, 2002	1719	546	2265
July 1, 2002-June 30, 2003	1905	838	2743
July 1, 2003-June 30, 2004	1763	1076	2839

Table 9 shows the number of assessments over time for anaphylaxis/anaphylactoid reactions, convulsions, elevated SGPT/ALT, liver lesions, low platelets, and immune-mediated hemolytic anemias (IMHA) that were possibly or probably related to ProHeart 6 administration. The annual number of assessments for anaphylaxis/anaphylactoid reactions decreased, but still remained relatively high in 2003-2004. The number of assessments for convulsions ranged between 110 and 126 annually. Assessments for the other clinical manifestations shown in Table 10 have increased over time. The clinical manifestations shown in Table 9 are described in more detail in the next section.

Table 9. Number of causality assessments for certain reported clinical manifestations that are possibly or probably related to the use of ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT Elevation	Liver Lesions	Low Platelets	IMHA
July 1, 2001 - June 30, 2002	704	110	34	9	26	14
July 1, 2002 - June 30, 2003	544	126	52	15	28	24
July 1, 2003 - June 30, 2004	487	118	92	37	52	26

Table 10 shows by year the number of dogs with ADEs that were possibly, probably, or definitely related to ProHeart 6 and the number of dog deaths that were possibly or probably related to ProHeart 6 by year. A label revision, which was approved on July 15, 2003, required the sponsor to add "and rare reports of death" to the post approval experience section of the product label and to send a Dear Doctor Letter. Despite these changes, the number of reported deaths, possibly or probably related to ProHeart, 6 increased each year since the product was marketed (Table 10). In addition, the number of dogs with heartworm infections that were possibly, probably, or definitely related to the ineffectiveness of ProHeart 6 also increased (Table 11).

Table 10. Number of dogs with reported ADEs that are possibly, probably, or definitely related to ProHeart 6 and number of reported dog deaths that are possibly or probably related to ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Number of Dogs	Number of Deaths
July 1, 2001 - June 30, 2002	1896	112
July 1 2002 - June 30, 2003	1814	148
July 1 2003 - June 30, 2004	1640	185

Table 11. Number of dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Number of Dogs
July 1, 2001 - June 30, 2002	8
July 1 2002 - June 30, 2003	164
July 1 2003 - June 30, 2004	208

Clinical Manifestations

This section provides additional information on anaphylaxis/anaphylactoid reactions, convulsions, SGPT/ALT elevations, liver lesions, thrombocytopenia, and immune-mediated hemolytic anemia reported as ProHeart 6 ADEs. STARS searches were done using correspondence dates of June 6, 2001 (date of ProHeart 6 approval) to September 1, 2004. Because only one clinical manifestation is addressed within each subsection, the number of assessments is equal to the number of episodes. Case examples for each clinical manifestation can be found in Appendix D.

Anaphylaxis/Anaphylactoid Reactions

Table 12 shows causality assessment categories for 1828 reported episodes of anaphylaxis/anaphylactoid reactions in dogs that received ProHeart 6. CVM determined that approximately one-half of the anaphylaxis/anaphylactoid reactions were probably drug-related and approximately one-half were possibly drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the episodes were: high (1338), medium (374), low (94), and unknown (22).

Table 12. Number of assessments for anaphylaxis/anaphylactoid reactions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	913
Possibly drug-related	907
Remotely drug-related	5
Information Lacking	3
Total	**1828**

For the 1820 episodes of anaphylaxis/anaphylactoid reactions determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (1741), fair (69), and

poor (3). The health status of dogs in the remaining 7 episodes is not known. In 816 episodes, dogs did not have concomitant drugs or vaccines and in 731 episodes, dogs had concomitant drugs and/or vaccines. The concomitant status for dogs in 273 episodes is not known.

Table 13 shows the number of anaphylaxis/anaphylactoid reaction assessments by time of onset. Eighty (80) percent of the episodes occurred within 3 hours of ProHeart 6 administration. Among the 1837 dogs involved in the 1820 episodes, there were at least 54 deaths that were possibly or probably related to ProHeart 6.

Table 13. Number of assessments by time of onset for anaphylaxis/ anaphylactoid reactions possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
< 15 minutes	374 (20.5%)
15 minutes to <1 hour	575 (31.6%)
1 to <3 hours	508 (27.9%)
3 to < 24 hours	296 (16.3%)
1 to <3 days	37 (2.0%)
3 to <7 days	8 (0.4%)
7 to <14 days	14 (0.8%)
14 to <30 days	3 (0.2%)
≥1 month	1 (0.1%)
Unknown	4 (0.2%)
Total	**1820**

The first ProHeart 6 label revision, which was approved on June 13, 2002, added to the product label the post-approval reported clinical manifestations of anaphylaxis/anaphylactoid reactions, depression/lethargy, urticaria, and head/facial edema. Although anaphylaxis/anaphylactoid reactions have declined (Table 9), they remain an ongoing problem with ProHeart 6. For the single marketing year of July 1, 2003 to June 30, 2004, there were 487 reported episodes with anaphylaxis/anaphylactoid reactions that were possibly or probably related to ProHeart 6 (Table 9). In contrast, there were only 97 reported episodes with anaphylaxis/anaphylactoid reactions that were possibly, probably, or definitely related to all monthly heartworm preventives combined for all marketing years (Table 4).

On January 14, 2004, the sponsor stated that anaphylactic reactions may be due in part to minimum residue solvents and that the elimination of these solvents might reduce these reactions. However, CVM continued to receive ADE reports for anaphylaxis/anaphylactoid reactions with zero residual solvent lots.

Convulsions

Seizures[1] were listed on the original ProHeart 6 product label because one dog in the clinical field trial experienced an increase in seizure frequency post-injection. Table 14 shows causality assessment categories for 405 reported episodes of convulsions in dogs following the administration of ProHeart 6. CVM determined that the majority of the convulsions were possibly (348) or probably (30) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the episodes were: high (88), medium (156), low (142), and unknown (19).

[1] Seizures are coded as "convulsions" in the CVM database.

Table 14. Number of assessments for convulsions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	30
Possibly drug-related	348
Remotely drug-related	23
Information Lacking	4
Total	**405**

For the 378 episodes of convulsions determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (302), fair (64), and poor (7). The health status of dogs in the remaining 5 episodes is not known. In 87 episodes, dogs did not have concomitant drugs or vaccines and in 215 episodes, dogs had concomitant drugs and/or vaccines. The concomitant status for dogs in 76 episodes is not known.

Table 15 shows the number of convulsion assessments by time of onset. Approximately one-half of the convulsion episodes occurred within 3 days after the administration of ProHeart 6. Among the 381 dogs involved in the 378 episodes, there were at least 61 deaths that were possibly or probably related to ProHeart 6.

Table 15. Number of assessments by time of onset for convulsions possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	62 (16.4%)
3 to <24 hours	51 (13.5%)
1 to <3 days	74 (19.6%)
3 to <7 days	66 (17.5%)
7 to <14 days	43 (11.4%)
14 to <30 days	31 (8.2%)
1 to <3 months	29 (7.7%)
≥3 months	13 (3.4%)
Unknown	9 (2.4%)
Total	**378**

There were more episodes with convulsions during the period of June 1, 2001 to September 1, 2004 for ProHeart 6 (Table 5) than for ivermectin products, for milbemycin products, or for selamectin products since their approvals (Table 4). The clinical manifestation "convulsions" was the most commonly reported neurologic sign among dogs treated with ProHeart 6. However, there were an additional 484 dogs with other types of neurologic signs that were possibly or probably related to ProHeart 6. Other neurologic signs reported include, but are not limited to ataxia, trembling, nervousness, confusion, and paresis.

Liver Signs

Between June 6, 2001 and September 1, 2004, there were more than 294 dogs reported to have liver-related clinical manifestations that were determined to be possibly

or probably related to ProHeart 6. Elevated SGPT/ALT and liver lesions noted on pathology reports were the most commonly reported liver-related clinical manifestations and will be the focus of this discussion.

SGPT/ALT Elevations

Table 16 shows the number of assessments, by causality assessment category, for SGPT/ALT elevations reported in 222 dogs following the administration of ProHeart 6. CVM determined that the majority of SGPT/ALT elevations were possibly (190) or probably (2) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the elevations were: high (49), medium (97), low (71), and unknown (5).

Table 16. Number of assessments for SGPT/ALT elevations reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	2
Possibly drug-related	190
Remotely drug-related	30
Information Lacking	0
Total	**222**

For the 192 SGPT/ALT elevations determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (149), fair (36), and poor (6). The health status of 1 dog is not known. Fifty (50) dogs did not receive concomitant drugs or vaccines and 112 dogs received concomitant drugs and/or vaccines. The concomitant status for 30 dogs is not known. Table 17 shows the number of assessments for SGPT/ALT elevations by time of onset. Approximately 58% of SGPT/ALT elevations occurred between 1 and 14 days after the administration of ProHeart 6. The 192 SGPT/ALT elevations occurred

in 192 dogs. There were at least 38 deaths among the dogs that were possibly or probably related to ProHeart 6.

Table 17. Number of assessments by time of onset for SGPT/ALT elevations possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	11 (5.7%)
3 to <24 hours	11 (5.7%)
1 to <3 days	31 (16.1%)
3 to <7 days	40 (20.8%)
7 to <14 days	41 (21.4%)
14 to <30 days	26 (13.5%)
1 to <3 months	16 (8.3%)
≥3 months	13 (6.8%)
Unknown	3 (1.6%)
Total	**192**

Liver Lesions

Table 18 shows the number of assessments, by causality assessment category, for liver lesions reported in dogs following the administration of ProHeart 6. CVM determined that the majority of liver lesions (65) were possibly drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the elevations were: high (16), medium (30), low (39), and unknown (3).

Table 18. Number of assessments for liver lesions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	0
Possibly drug-related	65
Remotely drug-related	23
Information Lacking	0
Total	**88**

For the dogs with liver lesions determined to be possibly drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (50) and fair (13). The health status of 2 dogs is not known. Thirteen (13) dogs did not have concomitant drugs or vaccines and 44 dogs had concomitant drugs and/or vaccines. The concomitant status for 8 dogs is not known.

Table 19 shows the time of onset for liver lesions possibly related to ProHeart 6 administration. Among the 65 dogs with liver lesions, at least 47 deaths were possibly or probably related to ProHeart 6. Necrosis or hepatocellular vacuolization was mentioned in some of these pathology reports. [d47]

Table 19. Number of assessments by time of onset for liver lesions possibly related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	2 (3.1%)
3 to <24 hours	7 (10.8%)
1 to <3 days	8 (12.3%)
3 to <7 days	5 (7.7%)
7 to <14 days	10 (15.4%)
14 to <30 days	9 (13.8%)
1 to <3 months	15 (23.1%)
≥3 months	8 (12.3%)
Unknown	1 (1.5%)
Total	**65**

There were more assessments for SGPT/ALT elevations and liver lesions for ProHeart 6 in the period June 1, 2001 to September 1, 2004 (Table 5) than there were for all monthly heartworm preventives combined for all marketing years (Table 4). Furthermore, Table 9 shows that the number of assessments for these two signs have increased over time for ProHeart 6.

Hematologic Signs

Several hematologic signs (clinical manifestations) were reported as ADEs for ProHeart 6. There were 551 dogs with hematologic signs possibly or probably related to ProHeart 6. Anemia (low red blood cell count) and thrombocytopenia (low platelet count) were among the most commonly reported hematologic signs. A number of dogs had both thrombocytopenia and hemolytic anemia.

Immune-Mediated Hemolytic Anemia

There were 225 dogs with anemia that was possibly or probably related to ProHeart 6. Some of these dogs were reported to have immune-mediated hemolytic anemia (IMHA), a life-threatening condition that occurs when an immune response causes the destruction of red blood cells.[33]

Table 20 shows the number of assessments, by causality assessment category, for IMHA reported in dogs following the administration of ProHeart 6. CVM determined that the majority of IMHAs were possibly (66) or probably (1) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the anemias were: high (20), medium (28), low (19), and unknown (3).

Table 20. Number of assessments for IMHAs reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	1
Possibly drug-related	66
Remotely drug-related	2
Information Lacking	1
Total	**70**

For the 67 dogs with IMHA that was possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (56), fair (10), and poor (1). Nineteen (19) dogs did not have concomitant drugs or vaccines and 34 dogs had concomitant drugs and/or vaccines. The concomitant drug/vaccine status for 14 dogs is not known. Table 21 shows the time of onset for IMHAs possibly or probably related to ProHeart 6 administration. Approximately one-half the IMHAs occurred between 1 week and 1 month following the administration of ProHeart 6. Among the 67 dogs with IMHA, there were at least 34 deaths that were possibly or probably related to ProHeart 6.

Table 21. Number of assessments by time of onset for IMHAs possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<24 hours	2 (3.0%)
1 to <3 days	2 (3.0%)
3 to <7 days	6 (9.0%)
7 to <14 days	15 (22.4%)
14 to <30 days	18 (26.9%)
1 to <3 months	18 (26.9%)
≥3 months	6 (9.0%)
Unknown	0
Total	**67**

Thrombocytopenia

Thrombocytopenia refers to a low platelet count. In dogs, thrombocytopenia is frequently caused by the destruction of platelets by an immune response (immune-mediated thrombocytopenia). [33]

Table 22 shows the number of assessments, by causality assessment category, for thrombocytopenia reported in dogs following the administration of ProHeart 6. There were 135 reported episodes with thrombocytopenia following ProHeart 6 administration. CVM determined that the majority were possibly (123) or probably (1) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the low platelet counts were: high (21), medium (61), low (48), and unknown (5).

Table 22. Number of assessments for thrombocytopenias reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	1
Possibly drug-related	123
Remotely drug-related	10
Information Lacking	1
Total	**135**

For the 124 thrombocytopenia episodes possibly or probably related to ProHeart 6, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (91), fair (28), and poor (4). The health status for the dog(s) in one episode is not known. In 26 episodes, the dogs did not have concomitant drugs or vaccines and in 76 episodes, the dogs had concomitant drugs and/or vaccines. The concomitant drug/vaccine status for dogs in 22 episodes is not known.

Table 23 shows the time of onset for thrombocytopenia possibly or probably related to ProHeart 6 administration. The times of onset for thrombocytopenia are similar to those for IMHA. Forty-three (43) percent of thrombocytopenias occurred between 1 week and 1 month following ProHeart 6 administration. The 124 thrombocytopenia episodes involved 125 dogs. There were at least 45 deaths among these dogs that were possibly or probably related to ProHeart 6.

Table 23. Number of assessments by time of onset for thrombocytopenia possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<24 hours	2 (1.6%)
1 to <3 days	11 (8.9%)
3 to <7 days	25 (20.2%)
7 to <14 days	29 (23.4%)
14 to <30 days	24 (19.4%)
1 to <3 months	23 (18.5%)
≥3 months	8 (6.5%)
Unknown	2 (1.6%)
Total	**124**

There were more assessments for IMHA and thrombocytopenia for ProHeart 6 in the period June 1, 2001 to September 1, 2004 (Table 6) than there were for all monthly heartworm preventives combined for all marketing years (Table 5). Table 9 shows that the number of assessments for low platelets has increased over time for ProHeart 6.

Conclusions

CVM has the responsibility for ensuring the safety of animal drugs. The sponsor of an animal drug product has the responsibility to demonstrate that the product is safe and effective prior to approval. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness under the labeled conditions of use. Most of the common adverse events may become known prior to approval. CVM has a post-approval monitoring system to detect adverse drug events that occur after marketing, i.e., when an animal drug is used in a larger and more diverse population.

If CVM determines that a marketed animal drug product is likely to be causing serious adverse effects, it must evaluate what steps are necessary to address the issues

raised by the adverse event reports. ProHeart 6 is used primarily to prevent heartworm infections in dogs. There are alternative products that are approved for use in dogs to prevent heartworm infections. The frequency of ProHeart 6 adverse drug events, the severity of the events, which include death, and the temporal association with administration of ProHeart 6 raise serious questions about the safety of this heartworm preventive product. These adverse drug events are particularly striking when compared to other marketed heartworm preventive products, including Fort Dodge Animal Health's monthly heartworm preventive. In working with FDAH to address the adverse events associated with ProHeart 6, CVM has requested three label revisions. Despite these changes, the agency has continued to receive a large number of serious adverse drug events related to ProHeart 6. Therefore, CVM has concluded that there are serious questions regarding the continued safety of ProHeart 6. Fort Dodge, at FDA's request, agreed to immediately cease production and recall Proheart 6 from the market until the safety concerns associated with the product are resolved.

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Appendix A. Causality Assessment Algorithm for Adverse Drug Events

1. Previous Experience With Drug:

+1 CM generally recognized to occur in this species at the dosage received.

0 CM is not generally recognized to occur in this species at the dosage received but has been previously reported in veterinary and/or human medicine.

Drug has limited accumulated clinical experience (time and/or quantity marketed).

-1 CM previously unreported and drug has substantial accumulated clinical experience (time and/or quantity marketed).

2. Alternative Etiologic Candidates:

+2 There is **no** good candidate or no change in a candidate which can explain the CM, exclusive of drug administration.

0 An alternative candidate(s) exists, but not a good one(s) which can **well** explain the CM.

CM commonly occurs spontaneously in this type of patient and situation, usually in the absence of any recognizable alternative candidate(s).

-1 There **is** a good candidate or a change in a candidate which can well explain the CM, exclusive of drug administration.

3. Timing of Events:

+1 Timing was consistent and as expected for this type of CM to this drug.

0 Do not know what timing to expect.

-2 Timing was inconsistent for this type of CM to this drug.

4. Evidence of Overdose:

+1 CM is clearly a dose-related type of manifestation, **and** there is unequivocal evidence that the amount of drug received was an overdose for this animal.

0 CM is not a dose related type of manifestation **or** there in no evidence of an overdose.

5. Dechallenge:

+1 CM diminished or disappeared after discontinuation of suspect drug or administration of a **specific** antidote.

CM is known to be dose-related, and CM diminished or disappeared after dosage reduction.

0 Dechallenge difficult, impossible, or inappropriate to assess.

A non-specific agent or maneuver (non-antidotal was administered that was directed against the CM and that usually produces the degree and rate of improvement observed in the case.

CM characteristically transient and episodic, and there is no established pattern episodes (regardless of what occurs after discontinuing the drug).

CM known to be dose-related, and CM did not diminish or disappear after dosage was reduced.

-1 CM did **not** diminish or disappear after discontinuation of suspect drug.

CM improved without dechallenge **and** the improvement **cannot** be attributed to the development of tolerance.

6. Rechallenge:

+1 CM unequivocally recurred or exacerbated after rechallenge.

0 There was no rechallenge attempted.

A non-specific agent or maneuver (non-antidotal) was administered that obscured the response of the CM.

CM failed to recur or exacerbate on rechallenge, **but** the dosage or duration of drug administration on rechallenge was substantially less than that suspected of causing the original CM.

Recurrence or exacerbation of CM was impossible to assess because it was progressing or was at a level of severity that any further increase would be difficult to appreciate.

-1 CM failed to recur or exacerbate on rechallenge.

The component scores above are then summed to reach a final causal score:

Scores	**Category of Association**
-9	Not applicable
-8	Information lacking
-7	No conclusion
-1 to -6	Remotely drug-related
0 to 2	Possibly drug-related
3 to 5	Probably drug-related
6 to 7	Definitely drug-related

-1	Ineffectiveness - Remotely drug-related
0 to 1	Ineffectiveness - Possibly drug-related
3	Ineffectiveness - Probably drug-related
6	Ineffectiveness - Definitely drug-related

Appendix B. Approved Monthly and 6-Month Heartworm Preventives

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ ANADA	Approval Date
Heartgard	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease. Heartgard® prevents heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection.	138-412	4/7/1987
Heartgard Chewables	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immits)* for one month (30 days) after infection .	140-886	8/9/1989
Heartgard Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immits)* for one month (30 days) after infection andfor the treatment and control of ascarids (*Toxocara canis, Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala*, *Ancylostoma braziliense)*.	140-971	1/15/1993
Advantage Duo	Ivermectin and Imidacloprid	Oral	Advantage DUO (imidacloprid/ivermectin) is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*, kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*). Advantqge DUO is recommended for dogs eight weeks of age or older.	141-208	9/27/2002
Iverhart	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease. IVERHART tablets prevent heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for one month (30 days) after infection.	200-270	11/30/2001
Ivermectin Chewable Tablets	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immits)* for a month (30 days) after infection.	200-297	6/18/2004

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ ANADA	Approval Date
Iverhart Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm diseases by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris* leonina) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala Ancylostoma braziliense*).	200-302	5/30/2001
Tri-Heart Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm diseases by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris* leonine) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma brazilense*).	200-338	8/13/2003
Interceptor	Milbemycin Oxime	Oral	INTERCEPTOR Flavor Tabs are indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis*, the control of adult *Ancylostoma caninum (hookworm)*, and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworms) and *Trichuris vulpis* (whilpworm) infections in dogs and puppies four weeks of age or greater and two pounds of body weight or greater.	140-915	6/14/1990
Sentinel	Milbemycin Oxime and Lufenuron	Oral	SENTINEL Flavor Tabs are indicated for use in dogs and puppies, four weeks of age or older, and two pounds of body weight or greater for the prevention of heartworm disease caused by *Dirofilaria immitis*, for the prevention and control of flea populations, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis*, and *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm) infections. Lufenuron controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.	141-084	4/10/1997

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ ANADA	Approval Date
ProHeart	Moxidectin (Tablets)	Oral	ProHeart (moxidectin) heartworm prevention tablets are indicated for once-a-month use in dogs to prevent infections by the canine heartworm, *Dirofilaria immitis,* and the subsequent development of canine heartworm disease.	141-051	5/27/1997
ProHeart 6	Moxidectin (Sustained Release)	Subcutaneous Injection	ProHeart 6 is indicated for use in dogs six months of age and olderfor the prevention of heartworm disease caused by *Dirofilaria immitis*. ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Unicinaria stenocephala*) infections.	141-189	6/6/2001
Revolution	Selamectin	Topical	Revolution is recommended for use in dogs six weeks of age or older for the following parasites and indications: Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Revolution is also indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) and for the control of tick infestations due to *Dermacentor variabilis*.	141-152	5/26/1999

Appendix C. ProHeart 6 Label, May 2003

(note, if difficulty viewing click “view” on the tools menu and then click “print layout”.

NADA 141-189, Approved by FDA

FORT DODGE®

ProHeart® 6
(moxidectin)

Sustained Release Injectable for Dogs

SAMPLE

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
ProHeart 6 (moxidectin) Sustained Release Injectable consists of two separate vials. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH.

PHARMACOLOGY
Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of *Streptomyces cyaneogriseus* subsp *noncyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 0.17 mg moxidectin/kg body weight is the tissue larval stage. The larval and adult stages of the canine hookworms, *Ancylostoma caninum* and *Uncinaria stenocephala*, are susceptible.

Following injection with ProHeart 6, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the six month dosing interval, residual drug concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

INDICATIONS
ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis*.

ProHeart 6 is indicated for the treatment of existing larval and adult hookworm *(Ancylostoma caninum* and *Uncinaria stenocephala)* infections.

DOSAGE AND ADMINISTRATION
Frequency of Treatment: ProHeart 6 prevents infection by *D. immitis* for six months. It should be administered within one month of the dog's first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes. When replacing another heartworm preventive product, ProHeart 6 should be given within one month of the last dose of the former medication.

ProHeart 6 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. However, persistent effectiveness has not been established for this indication. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 6 months.

Dose: The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.0227 mL/lb.). This amount of suspension will provide 0.17 mg moxidectin/kg bodyweight (0.0773 mg/lb.). To ensure accurate dosing, calculate each dose based on the dog's weight at the time of treatment. Do not overdose growing puppies in anticipation of their expected adult weight. The following dosage chart may be used as a guide.

DOSAGE CHART

Dog Wt.		Dose Volume	Dog Wt.		Dose Volume
lb	kg	mL/Dog	lb	kg	mL/Dog
11	5	0.25	77	35	1.75
22	10	0.50	88	40	2.00
33	15	0.75	99	45	2.25
44	20	1.00	110	50	2.50
55	25	1.25	121	55	2.75
66	30	1.50	132	60	3.00

Injection Technique: The two-part sustained release product must be mixed at least 30 minutes prior to the intended time of use (See **CONSTITUTION PROCEDURES** for initial mixing instructions). Once constituted, swirl the bottle gently before every use to uniformly re-suspend the microspheres. Withdraw 0.05 mL of suspension/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 mL should be administered in a single site. The location(s) of each injection (left or right side) should be noted so that prior injection sites can be identified and the next injection can be administered on the opposite side.

CONTRAINDICATIONS
ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

HUMAN WARNINGS
Not for human use. Keep this and all drugs out of the reach of children.

May be slightly irritating to the eyes. May cause slight irritation to the upper respiratory tract if inhaled. May be harmful if swallowed. If contact with the eyes occurs, rinse thoroughly with water for 15 minutes and seek medical attention immediately. If accidental ingestion occurs, contact a Poison Control Center or a physician immediately. The material safety data sheet (MSDS) contains more detailed occupational safety information.

PRECAUTIONS
Use with caution in sick, debilitated or underweight animals (see SAFETY).

ProHeart 6 should not be used more frequently than every 6 months.

The safety and effectiveness of ProHeart 6 has not been evaluated in dogs less than 6 months of age.

Prior to administration of ProHeart 6, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, ProHeart 6 is not effective for microfilariae clearance.

ADVERSE REACTIONS

In field studies, the following adverse reactions were observed in approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature.

Post-Approval Experience: Although not all adverse reactions are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toid reactions, depression/lethargy, urticaria, head/facial edema, and rare reports of death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

ANIMAL SAFETY

General Safety: ProHeart 6 has been safely administered to a wide variety of healthy dogs six months of age and older, including a wide variety of breeds, pregnant and lactating females, breeding males, and ivermectin-sensitive collies. However, in clinical studies, two geriatric dogs with a history of weight loss after the initial ProHeart 6 injection died within a month of the second 6 month injection. A third dog who was underweight for its age and breed and who had a history of congenital problems experienced lethargy following the initial injection of ProHeart 6. The dog never recovered and died 3 months later (see **PRECAUTIONS**).

ProHeart 6 administered at 3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in ivermectin-sensitive collies did not cause any adverse reactions. ProHeart 6 administered at 3 times the recommended dose did not adversely effect the reproductive performance of male or female dogs. ProHeart 6 administered up to 5 times the recommended dose in 7-8 month old puppies did not cause any systemic adverse effects.

In well controlled clinical field studies, ProHeart 6 was safely used in conjunction with a variety of veterinary products including vaccines, anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics and flea control products.

Injection Site Reactions: Injection site observations were recorded during effectiveness and safety studies. In clinical studies, ProHeart 6 was administered at six-month intervals to client-owned dogs under field conditions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

In a laboratory safety study, ProHeart 6 was administered at 1, 3 and 5 times the recommended dose to 7-8 month old puppies. Injection sites were clipped to facilitate observation. Slight swelling/edema at the injection site was observed in some dogs from all treated groups. These injection site reactions appeared as quickly as 8 hours post injection and lasted up to 3 weeks. A three-year repeated injection study was conducted to evaluate the safety of up to 6 injections of ProHeart 6 administered at the recommended dose (0.17 mg/kg) every 6 months. Mild erythema and localized deep subcuticular thickening were seen in dogs that received four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous panniculitis with microvacuolation. The only adverse reaction seen that was not related to the injection site was weight loss in one dog.

Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 5 months after injection.

CONSTITUTION PROCEDURES

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use.

Items needed to constitute ProHeart 6:
- Microspheres (vial 1)
- Sterile 20 mL syringe for transfer
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)
- Vehicle (vial 2)

Constitution of the 20 mL vial product.

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the unique vehicle from the vial. **There is more vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
7. Record the time and date of mixing on the microsphere vial.
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before every use, gently swirl the mixture to achieve uniform suspension. The microspheres and vehicle will gradually separate on standing.
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.
11. Refrigerate the unused product. The constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.

STORAGE INFORMATION

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 4 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 6 is available in the following two package sizes.

1. 5-Pack
NDC 0856-3670-25 – 20 mL vial product:
5 - 10% moxidectin sterile microspheres - 598 mg/vial
5 - Sterile vehicle - 17 mL/vial

2. 10-Pack
NDC 0856-3670-29 – 20 mL vial product:
10 - 10% moxidectin sterile microspheres - 598 mg/vial
10 - Sterile vehicle - 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 685-5656.

U.S. Patent No. 4,916,154 and 6,340,671

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

01283 Revised May 2003 3670E

Appendix D. Case Studies

Anaphylaxis/Anaphylactoid Reactions

The following examples represent dogs with anaphylaxis or anaphylactoid reactions that are possibly or probably associated with ProHeart 6.

1. **Case 200202319**

Signalment:

- Age: 8 months
- Breed: Mexican Hairless
- Gender: Neutered male
- Weight: 21 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Neutered on 4/16/02
- Date of Injection: 4/17/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: ketamine, Valium, isoflurane
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Probably drug-related

The dog recovered from surgery and received a ProHeart® 6 injection the next day in the hospital. He collapsed within 20 minutes and was transferred to an emergency clinic. Radiographs revealed no significant findings. He was treated supportively with intravenous fluids. The attending veterinarian was unable to stabilize his blood pressure, and the owners elected euthanasia.

2. **Case 200306896**

Signalment:

- Age: 3 years
- Breed: Schnauzer
- Gender: Spayed female

- Weight: 12.5 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/17/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Probably drug-related

The dog began to vomit within 20 minutes of the injection. She became depressed and collapsed shortly after injection. She was treated with epinephrine, Benadryl, dexamethasone, and intravenous fluids. She recovered initially, but died during the night.

3. **Case 200400552**

Signalment:

- Age: 7 years
- Breed: Wire Haired Fox Terrier
- Gender: Spayed female
- Weight: 24.6 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 1/22/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Progressed to severe condition, survived**
- Necropsy: Not applicable

Causality Assessment Category: Probably drug-related

The dog was depressed and lethargic for 48 hours after the injection and was taken to Tufts University Teaching Hospital. The attending veterinarian at Tufts found facial edema and swollen lymph nodes and diagnosed a delayed hypersensitivity adverse event to ProHeart® 6. The dog's condition progressed in 12 days to a more generalized adverse event including thrombocytopenia, prolonged partial thromboplastin time (PTT), painful abdomen, and elevated bilirubin. She was treated with tapering doses of Benadryl. The dog was discharged on 2/10/04.

4. **Case 200403348**

Signalment:

- Age: 8.5 years
- Breed: Alaskan Malamute
- Gender: Spayed female
- Weight: 104 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/29/04
- Dose: Underdosed by 0.16 mL
- Concomitant Vaccinations or Drugs: None
- Outcome: **Acute death**
- Necropsy: Acute anaphylactic shock

Causality Assessment Category: Possibly drug-relatedThe dog was found dead 12 hours post-injection. A post-mortem revealed venous congestion of the lungs and liver consistent with acute anaphylactic shock.

5. Case 200403885

Signalment:

- Age: 3 years
- Breed: Staffordshire Bull Terrier
- Gender: Female
- Weight: 62 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 6/18/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Probably drug-related

The dog began vomiting within 30 minutes of the injection. She became recumbent with pale membranes within 1 hour. She was given Benadryl and dexamethasone and recovered.

CVM also had concern about anaphylaxis/toid events reported among dogs that received ProHeart® 6 concurrently with a vaccine or another drug. The following examples represent a sample of cases with causality assessment scores of zero or above for anaphylaxis/anaphylactoid reactions in the concomitant drug and vaccine subgroup.

6. **Case 200200791**

Signalment:

- Age: 4 years
- Breed: Miniature Schnauzer
- Gender: Female spayed
- Weight: 19 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 2/11/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper vaccination
- Outcome: **Progressed with multiple clinical signs, recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog collapsed within 2 hours of injection, was treated with fluids, steroids and diphenhydramine, and released. She presented later that evening to the emergency clinic at Michigan State University (MSU) with a seizure. She recovered, but presented to her regular veterinarian the next day with a papular skin eruption on the neck and back and wheals on the head. She was referred to MSU for a skin biopsy. No biopsy results were submitted to CVM, but the dog was progressing well clinically on 4/16/02 re-evaluation.

7. **Case 200203569**

Signalment:

- Age: 3 years
- Breed: Pug
- Gender: Neutered male
- Weight: 25.6 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Overweight, arthritis
- Date of Injection: 6/5/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Carprofen

- Outcome: **Acute death**
- Necropsy: Acute anaphylaxis

Causality Assessment Category: Possibly drug relatedThe dog became agitated during a nail trim following the injection. He vomited, collapsed, arrested and died within 25 minutes. His body was transported to the University of Minnesota Veterinary Teaching Hospital for a post mortem examination; findings were consistent with acute anaphylaxis. The nail trim may have exacerbated the anaphylactic response due to endogenous epinephrine release.

Convulsions

The following examples represent cases involving convulsions that are possibly related to ProHeart® 6 injections in the absence of concomitant vaccinations or drugs.

1. Case 200103398

Signalment:

- Age: 2 years
- Breed: Yorkshire Terrier
- Gender: Male
- Weight: 3.2 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 7/21/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: Progressive neurological signs
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related (convulsion)
Remotely drug-related (encephalitis)

The dog developed convulsions and periorbital pruritus within 2 hours of ProHeart 6 injection. He was diagnosed with encephalitis of unknown origin. The cause of small dog encephalitis is not known; drugs are one etiologic explanation. [34]

2. **Case 200104935**

Signalment:

- Age: 7 years
- Breed: German Shepherd Mix
- Gender: male
- Weight: 100 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/15/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome**: Recovered, ongoing treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog presented with seizures 30 hours after injection. He was treated with phenobarbital and Valium. The dose of phenobarbital was decreased in late October. As of late November, no additional seizures were reported. The veterinarian listed differential diagnoses of idiosyncratic drug reaction or epilepsy.

3. **Case 200202452**

Signalment:

- Age: 18 months
- Breed: Pit Bull Terrier
- Gender: Neutered male
- Weight: 47.5 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/19/02

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered, ongoing treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

Vomiting, diarrhea, and inappetence began an hour after the injection and were ongoing for 3 days. He was examined on 4/22/02 and treated with Baytril, dexamethasone, and cimetidine. The dog began having seizures 9 days after injection. Blood tests showed elevated liver enzymes. He was treated with Valium and phenobarbital. On 5/5/02 (14 days after injection) the dog was trembling and had severe pain when he opened his mouth. A magnetic resonance imaging (MRI) test and a cerebrospinal fluid (CSF) tap identified no cause for the seizures.

4. **Case 200207752**

Signalment:

- Age: 3 years
- Breed: Golden Retriever
- Gender: Male
- Weight: 107 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/27/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered, onging treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog had a seizure 10 hours after injection. He had two more seizures over the next 24 hours and was treated with phenobarbital and Valium. He developed bloody diarrhea and vomiting at 2 weeks post injection and lost 5 pounds. The veterinarian tried to

discontinue phenobarbital in February 2003, but the dog had another seizure and was started on the phenobarbital again. No additional seizures were noted at a 2 month follow-up visit.

5. **Case 200301322**

Signalment**:**

- Age: 10 years
- Breed: Miniature Schnauzer
- Gender: Spayed female
- Weight: 30 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/1/03 (3rd dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had a seizure 4 days after she was given her third dose of ProHeart® 6 and developed elevated liver enzymes 7 days later. A veterinary neurologist developed a differential diagnosis that included a forebrain lesion due to encephalitis, neoplasia, or a cerebral vascular incident. The dog was euthanized without a necropsy 25 days following her injection.

6. **Case 200301797**

Signalment:

- Age: 2.5 years
- Breed: Weimaraner
- Gender: Spayed female

- Weight: Not provided

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/21/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Progressive neurological disease and visual impairment, survived**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

Twenty-four hours after injection, the dog developed bloody diarrhea, vomiting, ataxia and a head tilt. She progressed to a prancing gait and partial blindness and was referred to the Louisiana Statue University (LSU) veterinary school. Fungal and tick titers were negative. MRI revealed dilated optic vessels and subtle changes in the occipital area of the cerebrum, thalamus, and optic radiation. CSF tap revealed mild lymphocytic inflammation. Distemper titers were 1:80 indicating vaccination, infection, or exposure. No diagnosis was made and the dog was sent home on tapering doses of prednisone. When the owner tried to wean her off her medication, clinical signs returned.

7. **Case 200302409**

Signalment:

- Age: 18 months
- Breed: Papillon
- Gender: Neutered male
- Weight: 6.7 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/14/03 (2nd dose)

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Meningoencephalitis; cardiac lesions

Causality Assessment Category: Possibly drug-related (seizure)
Remotely drug-related (encephalitis, cardiac lesions)

This dog began to have seizures 48 hours after his second injection of ProHeart 6. He had two seizures one hour apart. On 4/29/03 he was started on phenobarbital. He had a seizure and died 16 days after the ProHeart®6 injection. Necropsy revealed severe necrotizing granulomatous and eosinophilic meningoencephalitis. Moxidectin levels in the brain were run and were not found at the limits of detection. In the heart, the right ventricle was dilated and flabby with dark red foci of the epicardium. Turk's procedure (a special histopathology stain) indicated right ventricular hypertrophy.

8. **Case 200404520**

Signalment:

- Age: 4 years
- Breed: Chihuahua
- Gender: Spayed female
- Weight: 7.4 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/14/04 (2^{nd} dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had one previous ProHeart® 6 injection two years prior. Three days after her second injection she presented for anorexia and lethargy. Bloodwork was normal. She was treated with hydroxyzine and Pet-Tinic vitamins. Four days after that (or 7 days post injection) she had a seizure. She was treated with diazepam and phenobarbital. She had a seizure and died two days later (9 days following injection).

The following examples represent cases involving convulsions that were possibly related to ProHeart® 6 injections in dogs that had received concomitant vaccines or drugs.

9. **Case 200105179**

Signalment:

- Age: 6 years
- Breed: Pug
- Gender: Female
- Weight: 25 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/29/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper and rabies vaccinations
- Outcome: **Died**
- Necropsy: Inconclusive (body was frozen)

Causality Assessment Category: Possibly drug-related

This dog had a seizure within 10 minutes of the ProHeart® 6 injection and vaccine administration. She was treated with fluids, Benadryl, and steroids. She recovered and went home, but later that evening she presented to an emergency clinic with difficulty breathing. She had another seizure and died. At necropsy, chronic cardiac changes were noted. Other organ changes were suggestive of shock but the necropsy was inconclusive because the body had been frozen.

10. **Case 200201651**

Signalment:

- Age: 3 years
- Breed: Mixed
- Gender: Neutered male
- Weight: Not recorded

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/11/02
- Dose: Not provided
- Concomitant Vaccinations or Drugs: Distemper, rabies, and Lyme vaccinations
- Outcome: **Euthanasia**
- Necropsy: Multifocal ischemia of the brain

Causality Assessment Category: Possibly drug-related

This dog had a seizure 6 days after the ProHeart® 6 and vaccine administration. He was euthanized 11 days after the injections when he failed to respond to treatment. A veterinary neurologist at Cornell University examined the brain, noting multifocal ischemic lesions which may have been secondary to the seizures. No evidence of inflammation was found to support a diagnosis of infectious disease or a post-vaccinal condition.

11. **Case 200103297**

Signalment:

- Age: 1.5 years
- Breed: Miniature Pinscher
- Gender: Male
- Weight: 13.5 lb

History:

- Heartworm Status: Negative
- Health Status: Good

- Concomitant Medical Conditions: None
- Date of Injection: 6/27/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Monthly imidacloprid for fleas
- Outcome: **Progressive neurological disease, survived**
- Necropsy: Not provided

Causality Assessment Category: Possibly drug-related

The dog's signs started with ataxia and incoordination 12 hours after ProHeart 6 injection and progressed to dysmetria, tremors, abnormal reflexes, and stiffness by 18 days. He was treated successfully through September and weaned off prednisone. A progress review in December 2001 indicated that he still had tremors when excited.

12. **Case 200207622**

Signalment:

- Age: 2 years
- Breed: Pit Bull Terrier
- Gender: Neutered male
- Weight: 66.4 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/13/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper, rabies, and Lyme vaccinations
- Outcome: **Ongoing seizure disorder**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog started to vomit and have diarrhea within an hour of the ProHeart® 6 injection and vaccination. He had a seizure 1 day post –injections. The seizures returned in March and he has continued to see a neurologist for repetitive seizures. At the last follow-up, he

was on potassium bromide, Valium, and phenobarbital and was having seizures approximately every two weeks.

Liver Signs

The following examples represent cases involving liver lesions noted on biopsy or necropsy (PR-Liver) or SGPT/ALT elevations that were possibly related to ProHeart 6.

1. **Case 200202432**

Signalment:

- Age: 3 years
- Breed: Labrador Retriever
- Gender: Spayed female
- Weight: 71 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Mild atopy (skin allergies)
- Date of Injection: 1/5/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Benadryl as needed for atopy
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog began vomiting and collapsed 3 days after the injection. She was taken to an emergency clinic where she was found to be anemic and tachycardic. She also had elevated liver enzymes. She was treated with fluids and steroids. She improved and was re-examined the next day by her regular veterinarian who ruled out toxins and Addison's disease. No alternative etiologic candidate was found that explained her clinical manifestations.

2. **Case 200206333**

Signalment:

- Age: 4 years

- Breed: Pit Bull Terrier
- Gender: Male
- Weight: 58 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/8/02
- Dose: Underdosed by 0.20 mL
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had bloody diarrhea and began vomiting within 10 minutes of the injection. By 2 hours his condition had progressed to collapse, cyanosis, and pulmonary congestion. He was sent to an emergency referral clinic where he was treated with crystalloids, cefazolin, enrofloxacin, famotidine, and sucralfate. He failed to improve, became oliguric, and was referred to a specialist. His SGPT/ALT was as high as 20,773. He died by day 3 following the injection. He was included in both the anaphylaxis/anaphylactoid reaction category and the liver category.

3. **Case 200303279**

Signalment:

- Age: 10 years
- Breed: Labrador Retriever
- Gender: Spayed female
- Weight: 72 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/20/03

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Survived**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog was lethargic and anorexic on the evening of her first injection. By the third day following injection, she was jaundiced and diagnosed with elevated liver enzymes. Liver biopsy revealed chronic active hepatitis.

4. **Case 200401208**

Signalment:

- Age: 3 years
- Breed: Jack Russell Terrier
- Gender: Spayed female
- Weight: 17 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 8/14/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered after several months**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog presented 2 weeks after injection with vomiting, anorexia, and depression. She was diagnosed at an emergency veterinary center with elevated liver enzymes and a heart murmur. She was extensively evaluated by two veterinarians and a specialist and her workups included radiographs and ultrasound examination. No other cause for her condition was found. She was treated supportively with fluids, amoxicillin, and metronidazole and gradually improved over 60 days.

5. **Case 200303623**

Signalment:

- Age: 11 years
- Breed: Australian Cattle Dog
- Gender: Neutered male
- Weight: 32 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 6/3/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Multiple organ failure secondary to acute myocardial degeneration

Causality Assessment Category: Possibly drug-related

This dog showed signs of vomiting and lethargy 4 days after injection. His blood work revealed elevated creatinine and elevated liver enzymes and he was treated supportively with intravenous fluids and antibiotics. He tested negative for antifreeze poisoning and leptospirosis. He failed to improve and was euthanized at 2 weeks. At necropsy he was noted to have myocarditis, pneumonia, kidney tubular mineralization, ulceration of the stomach, endocardiosis, and mild multifocal hemorrhages of the brain. A veterinary cardiac pathologist reviewed the cardiac slides and diagnosed acute myocardial degeneration not thought to be related to hypoxia or epinephrine. The cause of the acute myocarditis could not be determined. Multiple organ failure was thought to be secondary to the cardiac condition.

6. **Case 200202608**

Signalment:

- Age: 6 years
- Breed: Maltese
- Gender: Spayed female

- Weight: 11.5 lb

History:

- Heartworm Status: Not provided
- Health Status: Fair
- Concomitant Medical Conditions: Mass in bladder, urinary tract infection
- Date of Injection: 4/26/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Baytril
- Outcome: **Euthanasia**
- Necropsy: Hepatocellular degeneration, encephalomalacia

Causality Assessment Category: Possibly drug-related

This dog presented for a urinary tract infection. The attending veterinarian diagnosed a bladder mass by palpation and ultrasound and prescribed Baytril. It is not clear exactly when the Baytril was started, but two hours after the ProHeart 6 injection, she was noted to be lethargic. Forty-eight hours later she had a seizure. She was treated with Valium and phenobarbital and the seizures stopped. She was transferred the next day to her regular veterinarian who noted elevated bile acids and elevated bilirubin. An MRI indicated diffuse infiltrative disease of the cerebral cortex. The dog was euthanized. A necropsy indicated a leiomyoma of the bladder which was pre-existing according to the history. The liver lesion was described as hepatocellular degeneration. The brain lesion was described as laminar cortical necrosis of the grey matter; most likely due to hypoxia. This dog had strong temporal drug association for neurologic and hepatic signs as well as neurologic signs that were consistent with what has been observed in other small breeds such as Yorkshire Terriers and Pugs (discussed previously under convulsions).

Hematologic Signs

The following examples represent cases of immune-mediated hemolytic anemia (IMHA) and/or thrombocytopenia possibly related to ProHeart 6.

1. Case 200103479

Signalment:

- Age: 5 years
- Breed: Australian/Border Collie Mix

- Gender: Neutered male
- Weight: 52 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 7/5/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog presented for lethargy and depression 14 days post-injection and was diagnosed with immune-mediated hemolytic anemia the next day. He was treated with Oxyglobin® (artificial hemoglobin), steroids, and antibiotics but did not respond. He was euthanized 12 weeks after his ProHeart 6 injection.

2. Case 200200772I

Signalment:

- Age: 12 years
- Breed: Yorkshire Terrier
- Gender: Spayed female
- Weight: 12 lb

History:

- Heartworm Status: Not mentioned
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 1/11/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog was diagnosed with immune-mediated hemolytic anemia 27 days after injection. She had a packed cell volume of 10% and died overnight at the local veterinary emergency clinic.

3. Case 200201234

Signalment:

- Age: 1 year
- Breed: Labrador Retriever Mix
- Gender: Neutered male
- Weight: 67 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 2/26/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog vomited and was depressed 6 hours after injection and was treated with dexamethasone, Benadryl, and fluids. Eight days later, he was diagnosed with immune-mediated hemolytic anemia. He tested negative for Lyme and Ehrlichia. He was treated with prednisone and Immuran and recovered.

4. Case 200203935I

Signalment:

- Age: 5 year
- Breed: Golden Retriever
- Gender: Neutered male
- Weight: 77 lb

History:

- Heartworm Status: Not provided

- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/13/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Unknown**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related (IMHA and low platelets)

This dog presented with exercise intolerance 5 weeks after ProHeart 6 injection. Blood tests showed a Coombs' Positive hemolytic anemia and thrombocytopenia. He was treated with cyclosporine and prednisone. The outcome of the case was not provided.

5. Case 200303433

Signalment:

- Age: 2 years
- Breed: Dachshund
- Gender: Neutered male
- Weight: 40 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Obesity; narcolepsy
- Date of Injection: 5/26/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Centrilobular hepatic necrosis; pulmonary vascular thrombosis

Causality Assessment Category: Possibly drug-related

This dog presented 34 days after his ProHeart 6 injection with anorexia and lethargy. His hematocrit on presentation was 11%. He had a positive slide agglutination test and elevated serum bilirubin. He was treated with prednisone, but died two days later. Necropsy revealed centrilobular hepatic necrosis

due to severe anemia. He also had cholestasis, hemosiderosis of the spleen, and pulmonary vascular thrombosis.

6. Case 200305624

Signalment:

- Age: 3 years
- Breed: Poodle
- Gender: Spayed female
- Weight: 15 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/22/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog was diagnosed with immune-mediated hemolytic anemia 7 days after ProHeart 6 injection. Her tick panel was negative. She was treated with azathiaprine, prednisone, doxycycline, and cyclosporine and two whole blood transfusions. She gradually improved and by six months post-injection, was off all medications.

7. Case 200200725 I

Signalment:

- Age: 11 years
- Breed: Pit Bull
- Gender: Spayed female
- Weight: 21 lb

History:

- Heartworm Status: Not provided
- Health Status: Good

- Concomitant Medical Conditions: Grade 3 heart murmur
- Date of Injection: 1/29/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper Vaccination
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog presented to an emergency clinic 8 days after her injections with pale mucous membranes. Her packed cell volume was 8.5%, and she was diagnosed with immune-mediated hemolytic anemia. She was Coombs', Lyme, and Ehrlichia negative and was treated with a blood transfusion and prednisone. She was euthanized at day 33 post-injection.

8. **Case 200307034**

Signalment:

- Age: 6 years
- Breed: Beagle mix
- Gender: Neutered male
- Weight: 50 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 9/27/03 (4th dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog developed a hot spot (pyoderma of the skin) at the tail base 2 hrs after his fourth ProHeart 6 injection and was treated successfully with gentamycin spray. He returned to the veterinarian 7 weeks later with a history of anorexia which started an unknown

number of days prior. He was febrile and weak and was diagnosed with immune-mediated hemolytic anemia (IMHA). Coombs test and tick panels were negative. His chemical profile was normal. He began a course of doxycycline, metronidazole, and increasing doses of prednisone. By 4 months, signs progressed to include elevated liver enzymes, bloody diarrhea, and vomiting. This dog was transferred to Purdue University and was further treated for blood in the stool. An endoscopic exam revealed ulceration of the gastrointestinal tract. Biopsy indicated mild suppurative inflammation of the gastric mucosa. No further follow-up information was provided.

9. Case 200202652 I

Signalment:

- Age: 3 years
- Breed: Rottweiler
- Gender: Spayed female
- Weight: 85 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/1/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper-Corona and Rabies Vaccinations
- Outcome**: Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog presented 26 days after ProHeart 6 injection and vaccination to a local emergency clinic for lethargy and depression of unknown duration. On physical examination, she was icteric. Her packed cell volume was 8%, and she had a positive slide agglutination test. She was treated with a blood transfusion, prednisone, and antibiotics.

10. Case 200205461

Signalment:

- Age: 8 years
- Breed: Keeshond
- Gender: Neutered male
- Weight: 45 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/9/02 (2nd dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome**: Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related (IMHA and low platelets)

There were no reported problems after the initial dose of ProHeart 6 on 11/2/01. This dog presented with depression and lethargy 14 weeks after the second injection. His PCV was 11% with agglutinating red cells. Platelets were estimated at 22,000. He was treated with two blood transfusions, prednisone, and cytoxin but died in 3 days.