

FDAH Adverse Event Report Re-analysis

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Fort Dodge Animal Health

FDAH Adverse Event Collection

- Professional Services Department
 - Technical Support
 - Adverse Event Investigations
 - Regulatory Compliance
 - Customer Support
- 28 DVMs with extensive clinical practice prior to joining industry
- 3 PhDs, 7 Vet Techs, 9 Support Staff

FDAH Adverse Event Collection

- All reports of suspected adverse events are investigated
- To improve the quality of data collected, FDAH routinely pays for diagnostic services including specialist referrals
- All reports received, regardless of causality, are recorded and submitted to CVM

FDAH Adverse Event Collection

- Report Categories
 - Injection Site Report
 - Allergy Report
 - Signs \leq 48 hours & consistent with allergy for species
 - Non-Allergy Report
 - Lack of Efficacy Report

Medical Association Assessment

- Based on VICH approved draft guidelines
- Each animal event assessed as a whole
- Three categories
 - Medical Association Possible
 - Product is at least one of equally plausible explanations for the event
 - All events are initially assigned to possible category

Medical Association Assessment

- Medical Association Unlikely
 - Sufficient information exists to establish event is not likely to have been associated with product, or there are other more plausible explanations
- Medical Association Probable
 - All the following must be met,
 - Reasonable association in time
 - Adverse event is reasonable given the known pharmacology and toxicology of the drug
 - No other equally plausible explanation

Comparison to Other Products Is Difficult

- Monthly oral products
 - Administered at home by owner as “treats”
 - Rates of use are dissimilar and difficult to know
- Different companies have a variety of systems to collect, investigate, quantify, and submit adverse observations as adverse event reports

Over-Reporting Bias

- For ProHeart 6, biases that may have stimulated reports of adverse observations are:
 - ProHeart 6 is an innovative sustained-release product
 - ProHeart 6 is administered parenterally by veterinarians
 - Two “Dear Doctor” letters discussing ProHeart 6 safety issues
 - Widely-disseminated news reports and website postings critical of ProHeart 6

Over-Reporting Bias

- Practitioner presented with diagnostic dilemma
 - Oral Preventive
 - History rarely includes heartworm preventive administration regardless of diagnostic outcome
 - Veterinarian does not make connection that preventive was given within last month
 - ProHeart 6
 - Veterinarian knows when ProHeart 6 was given
 - Likely to make temporal link to ProHeart 6
 - Leads to company contact for assistance
 - Report submitted to CVM

Total AERs By Year

<u>Active</u>	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2003 Market Share</u>
Ivermectin + pyrantel	73	339	2331	37%
ProHeart 6	677	2090	1604	24%
Milbemycin	113	102	1470	21%

CVM Annual AER Summary

- Number of reports for monthly preventives is lower in 2001 and 2002
- In 2003, reporting of AERs for ProHeart 6 is comparable to that of the leading heartworm preventives



AERs by Year Excluding Inefficacy

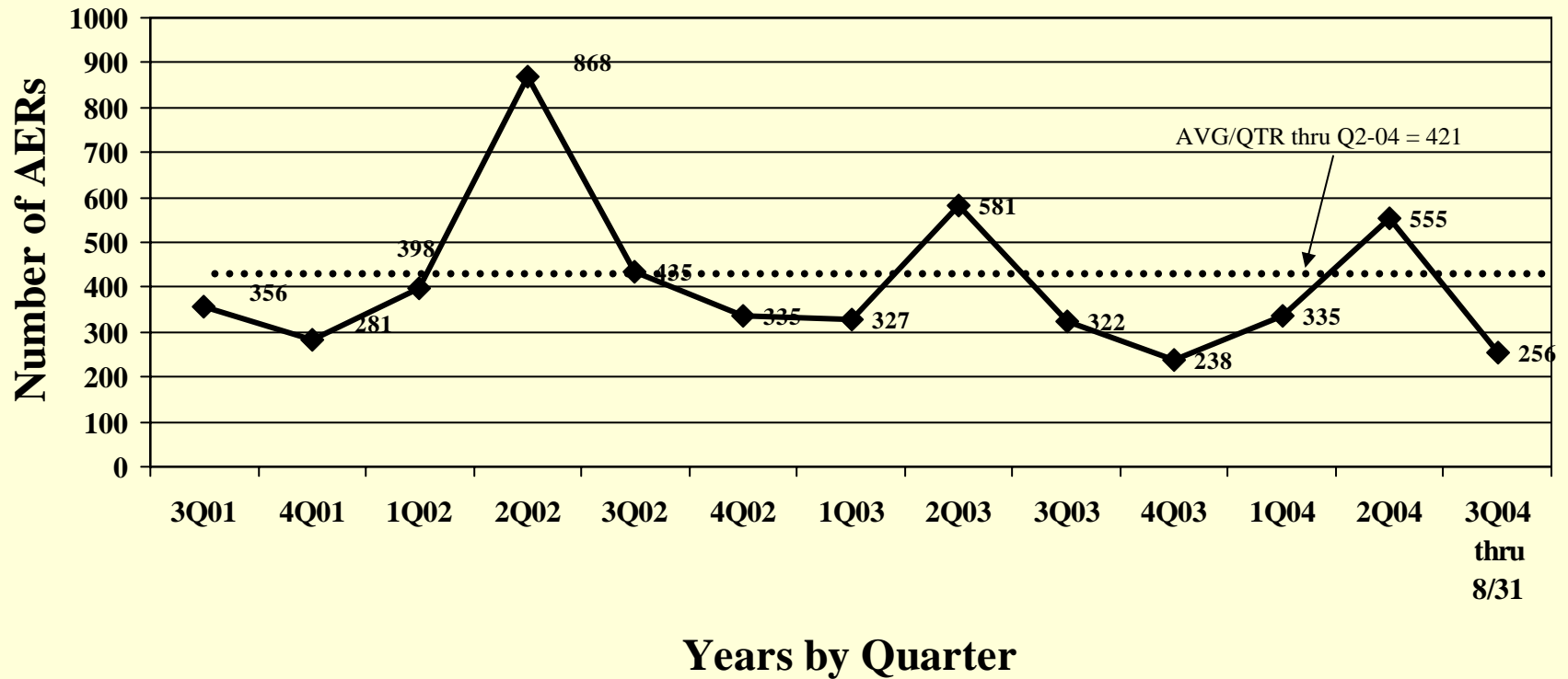
<u>Active</u>	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2003 Market Share</u>
Ivermectin + pyrantel	52	144	2194	37%
ProHeart 6	677	2020	1408	24%
Milbemycin	113	102	722	21%

CVM Annual AER Summary

- When inefficacy reports are excluded, the reporting rate for ProHeart 6 remains comparable to that of leading heartworm preventives



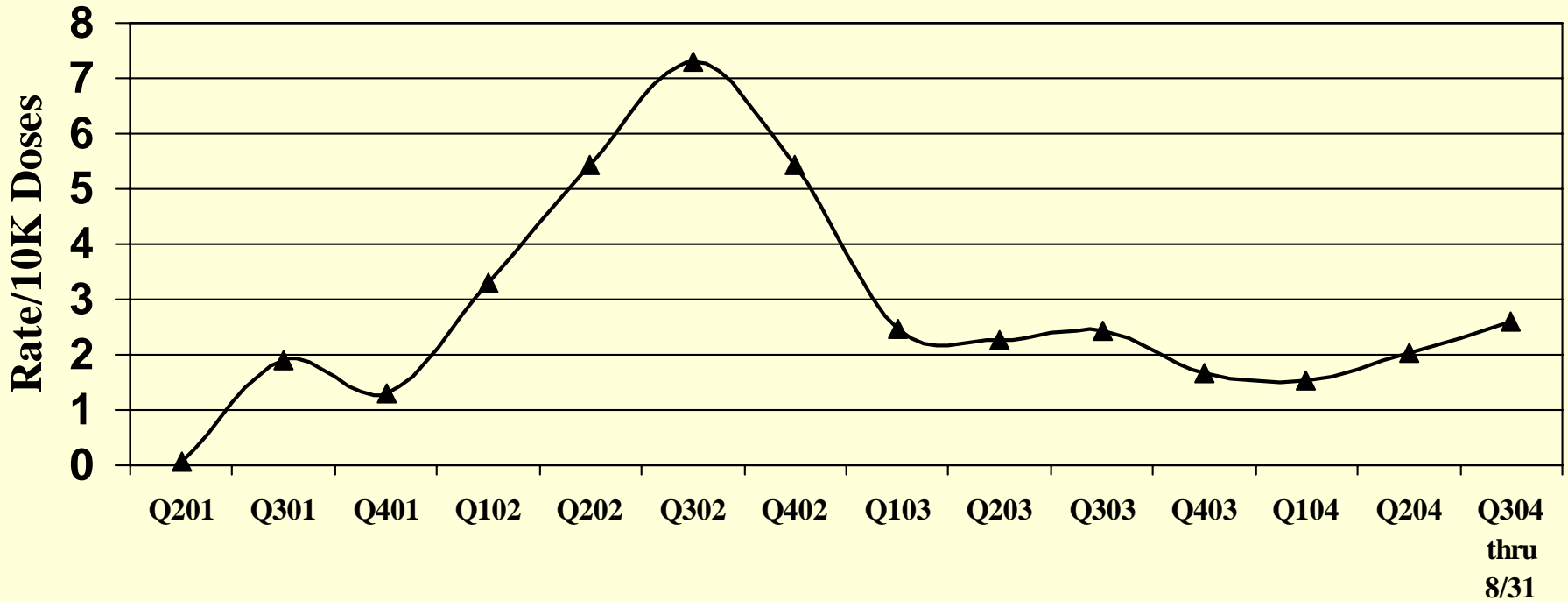
Number of AERs by Quarter



Reporting Rate

- Total numbers of AERs, while valuable, fail to estimate incidence of the event and fail to account for change in use of product
- Reporting rates are calculated by dividing the number of AERs by the number of doses sold in the same period
- Reporting rate provides a better estimate of incidence

Reporting Rate By Quarter



June 01 – May 02 2.45 per 10,000

June 02 – May 03 4.35 per 10,000

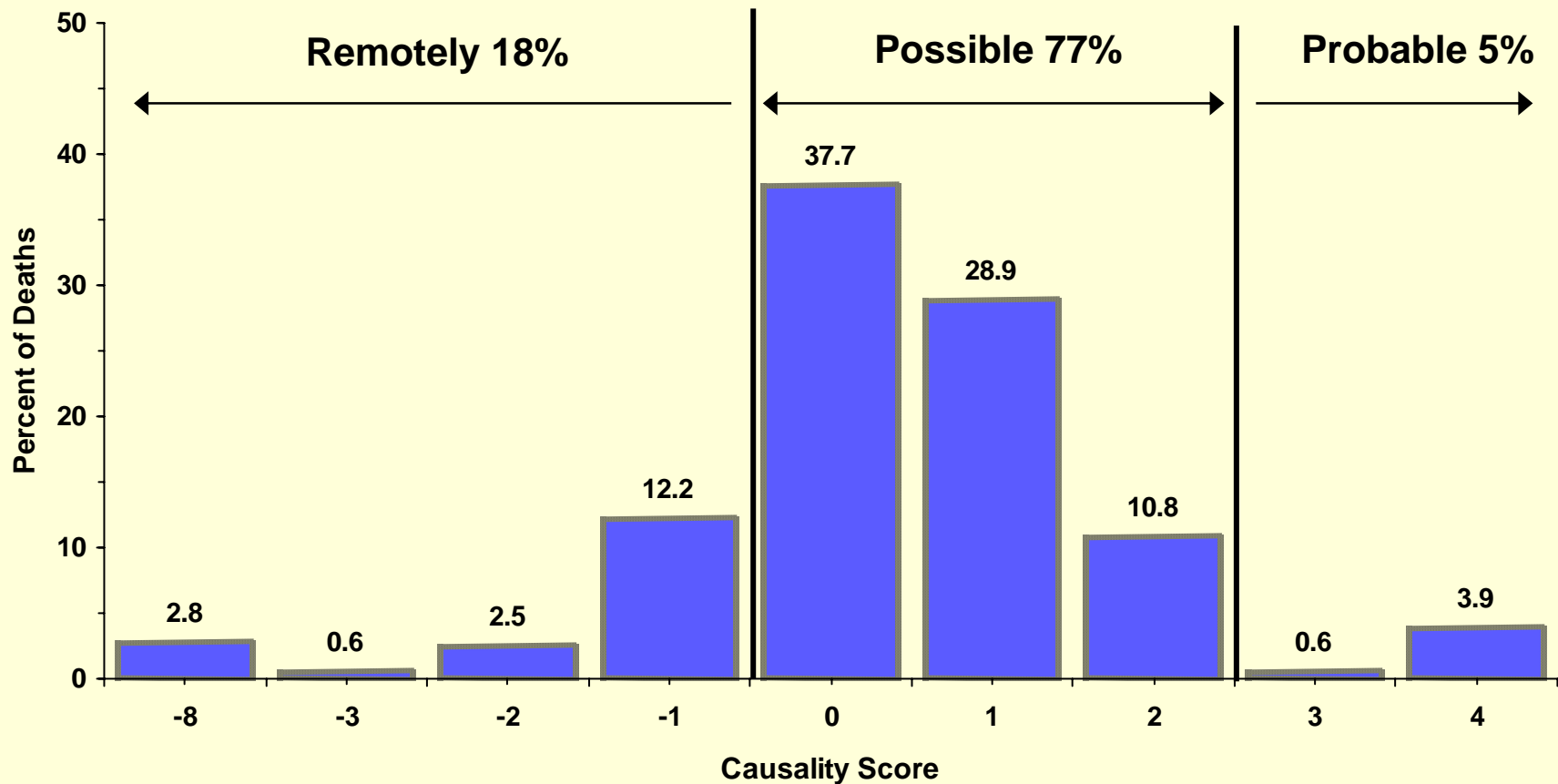
June 03 – May 04 2.13 per 10,000



Reports Involving Death

- FDA previously presented that there are 485 deaths that are at least possibly related to ProHeart 6
- FDAH was able to review the FDA's causality assessments in 353 of these reports

CVM Causality Assessment Scores for Deaths



Period covered: June 2001 through May 2004

Reports Involving Death

- FDA assesses 5% as “probably related” to ProHeart 6 (FDA score 3-4)
- FDA assesses 77% as “possibly related” to ProHeart 6 (FDA score 0-2)
- Should “possibly related” assessments support market recall?

Reports Involving Death

- Scientifically implausible events should be disregarded in conducting a meaningful review
 - Remove events with concurrent vaccination
 - Remove events with tumors (< 6 weeks)
 - Remove events with FDA causality of zero
 - 38% of events
 - Remove events with incorrect causality assessment

FDA Causality Assessments

- FDAH carefully reviewed a subset of the available FDA assessment reports
- In 1/3 of these reports, the FDA assessed events as “possibly related” while FDAH assessed these events as “remotely related”
- 2 examples
 - Dog with hemorrhagic episode; found to have significant levels of rodenticide in liver; FDA assessed as “possibly related”
 - Dog presented with pain in abdomen 4 months post-ProHeart 6; dog was euthanized and necropsied – hemangiosarcoma of liver diagnosed; FDA assessed as “probably related”

ProHeart 6 Death Reports in Context

- ProHeart 6 mortality rate
 - 500 per 12 million dogs per 2.5 years
 - 20 per 1 million dogs per year
- General canine population mortality rate
 - 5% per year
 - 50,000 per 1 million dogs per year
- Given limitations of passive AE reporting systems, the level of death reported with ProHeart 6 is less than the expected mortality rate in dogs

FDAH AER Categories

- Allergy Reports (n = 2652)
 - Signs include anaphylaxis, urticaria, itching
 - Most occur within 48 hours of administration
- Systemic (non-allergy) Reports (n = 2510)
 - Could involve any body system
 - Signs not typical of “allergy”
 - Time period not designated
 - AERs in this category may have allergic etiology

Allergy AERs

- Reporting rate is low
 - 1.26 per 10,000 doses sold
- > 80% allergic events are self-limiting and dog returns to normal
- Relative frequency decreases over time
- No breed predilection observed
- Reporting rate similar to FDAH vaccines and other common veterinary products

Systemic AER

- FDA has raised concerns about multiple body systems
 - Anaphylaxis
 - Convulsions
 - Liver SGPT/ALT
 - Liver lesions
 - Low Platelets
 - IMHA
- It is widely recognized that
 - When products cause toxicity it is expected that a single/small number of target organs is affected
 - In contrast, the wide variety of suspected adverse syndromes assigned to ProHeart 6 is inconsistent with established toxicological principles.

Non-Allergy AERs

- Expert review by body system
 - Neurologic: Alexander deLahunta, DVM, PhD, DACVIM, Neurology
 - Hematologic: Alan Rebar, DVM, PhD, DACVP, Clinical Pathology
 - Hepatic: Alan Rebar, DVM, PhD, DACVP, Clinical Pathology
 - Neoplasia: Philip Bergman, DVM, PhD, DACVIM, Oncology

Conclusions AER Analysis

- Independent experts and FDAH conclude majority of AERs are:
 - Not causally related to ProHeart 6 and reflect the normal range of diseases occurring in the dog population



Summary and Conclusions

- Moxidectin based products for use in veterinary medicine are registered in over 70 countries.
- Extensive toxicology studies were conducted in mice, rats, and dogs to support the approval of moxidectin for use in food-producing animals
- In a 1-year dog toxicology study, the daily dosage of moxidectin resulting in a monthly moxidectin exposure that is 454-fold greater than dogs administered the recommended dose of ProHeart 6 resulted in no toxicologically significant findings



Summary and Conclusions

- The rate of submission of initial ADE reports to CVM decreased in 2003 and 2004, compared with 2002
- ProHeart 6 is subject to substantial over-reporting bias
- Even with over-reporting bias and when corrected for market share the number of AERs associated with ProHeart 6 is similar to major competitors
- ProHeart SR 12 comparison to ProHeart 6 demonstrates similar reporting rates of AERs with an apparently lower reported rate of death

Summary and Conclusions

- While CVM identified 485 reports of death associated with ProHeart 6, FDAH estimates that only 5% of these reports were scored by CVM as “probably related” to ProHeart 6
- The vast majority of allergic events are self-limiting, and the rate of allergic reports is low and decreasing
- The vast majority of the non-allergic events are not causally related to ProHeart 6, and likely reflect the normal range of disease occurring in canine population

Summary and Conclusions

- Dr. Glickman and colleagues recently conducted a unique study that evaluated over 7 million dog encounters at veterinary hospitals from 42 states. This landmark study in veterinary epidemiology demonstrated that:
 - Concurrent use of vaccines demonstrates significant impact on AE rates
 - the safety profile of ProHeart 6 is similar to 2 monthly heartworm preventives

Summary and Conclusions

FDAH concludes that ProHeart 6 is a safe and effective product for prevention of heartworm disease

