RE: DOCKET NUMBER 2004D-0468

DRAFT GUIDANCE FOR DRUG SPONSORS ON NSAIDS FOR USE IN ANIMALS AVAILABLE FOR REVIEW AND COMMENT

To: **VIA REGULAR MAIL**
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA EMAIL: (lwilmot@cvm.fda.gov)
Dr. Linda Wilmot
Center for Veterinary Medicine (HV-114)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855
(301) 827-0135

RE: DOCKET NUMBER 2004N-0559

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

To: Kimberly Littleton Topper
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Email: **topperk@cder.fda.gov**

Fax: 301-827-6801

NSAIDS IN VETERINARY MEDICINE TODAY

DERAMAXX: A COMPREHENSIVE DOCUMENTATION OF PROBLEMS

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Prepared February 1, 2005

DERAMAXX - FDA CHRONOLOGY

On 8/21/02 Deramaxx received FDA approval "for the control of post operative pain and inflammation associated with orthopedic surgery in dogs." [1]

Testing to that point included the study of only 217 animals supposedly representative of 43 breeds, however, it should be mentioned that all toxicity and safety studies were performed on one breed, namely beagles, only. [2]

The 2 week Pharmacokinetics and Toxicity Study involved 12 beagles. All dogs survived to the end of the study. Conclusions were: (1) Non linear elimination of deracoxib occurs at doses of 10 mg/kg and above; (2) Elevated doses > 25 mg/kg are associated with COX-1 inhibition as evidenced by gastrointestinal signs; (3) The frequency and severity of the gastrointestinal lesions increased with escalating doses. The gastrointestinal lesions reported in deracoxib treated dogs at exaggerated doses are consistent with known non steroidal anti-inflammatory drug (NSAID) induced adverse events.

The 21 day Safety study involved 40 beagles. All dogs survived to study termination. There was a dose related increase in BUN values associated with administration of deracoxib tablets at all doses. No clear dose or test article relationship could be determined for histopathological changes noted.

The 13 week Capsule Study in Dogs with a 4 week Recovery period involved 48 beagles. Its purpose was: (a) To evaluate subchronic toxicity of deracoxib when administered to dogs; (b) To evaluate the reversibility of any toxic effects following a 4 week recovery period; ©) To determine absorption of the test article and the relationship of plasma concentration with dosage and duration of dosage. It was noted that 1 dog died of bacteria septicemia associated with renal abscess. Conclusions were that Deracoxib administered in capsules once daily for a period of 13 weeks, at doses up to 8 mg/kg body weight did not produce toxicity in HEALTHY (emphasis added) dogs; and that the relationship between deracoxib administration and a renal abscess in one dog given 8 mg/kg is not clear. NO WHERE IS THE REVERSIBILITY OF ANY TOXICITY DISCUSSED, NOR IS IT MENTIONED THAT ALL DOGS SURVIVED TO THE END OF THE STUDY.

Additionally, dosage instructions at this time were "3-4 mg/kg/day (1.4-1.8 mg/lb/day) as a single daily dose, **as needed for seven days**".

Thus, Deramaxx was approved for " the control of post operative pain and inflammation associated with orthopedic surgery in dogs."

Thereafter, and on January 16, 2003, the FDA objected to "Novartis' dissemination of promotional materials that are in violation of the Federal Food, Drug and Cosmetic Act (FDCA) and the FDA's applicable implementing regulations." More specifically, the letter referred to Drug Experience Reports dated August 30 through September 17, 2002, concerning Deramaxx. The FDA had received a number of industry and veterinarian complaints regarding the misleading claims in Novartis' September 9, 2002

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[1] **http://www.fda.gov/OHRMS/DOCKETS/98fr/03-29744.pdf**

[2] **http://www.fda.gov/cvm/efoi/section2/141-203.pdf**

letter to veterinarians. [3]

The statement "targeting the COX-2 enzyme while sparing the COX-1 enzyme" and similar statements throughout the promotions suggested that this conclusion had clinical significance. This statement was based upon in-vitro studies using cloned canine cyclooxygenase, the clinical relevance of which had not been shown. Novartis thus violated 21 C.F.R. Section 202.1(e)(3)(1) which requires that an otherwise misleading statement must include the appropriate qualification in the same part.

The FDA additionally objected to the opening paragraph of the letter which claimed Deramaxx as the "first and only....Coxib class drug" as misleading. Novartis' characterization failed to identify the product as NSAID and did not place appropriate recognition that Coxib was a subclass of the NSAID class of drugs. FDA approved labeling required the phrase "non-steroidal, anti-inflammatory of the coxib class"

The FDA concluded that this promotional activity minimized risks and implied a safer more effective product than other drugs in the same drug class. It noted particular concern because these specific limitations were discussed with HFV-110 during the application review, YET DESPITE DOCUMENTED VERBAL ASSERTIONS THAT IT WOULD NOT, NOVARTIS PROMOTED THE COX-2 VS. COX-1 SELECTIVITY OF THE PRODUCT.

The FDA requested that Novartis immediately cease dissemination of these and similarly violative promotional pieces and to promote it's product only in accord with the labeling provided in the approved application.

On February 11, 2003, the FDA authorized the new and expanded use of Deramaxx. Dosing changes accompanied each use. The field study tested 209 client owned dogs representing 41 different breeds for 43 days. Only 105 dogs received Deramaxx at the dosage of 1-2 mg/kg (0.45 - 0.90 mg/lb) administered once daily. [4]

Lameness assessments together with owner evaluations are offered as proof of the effectiveness of Deramaxx for the control of pain and inflammation associated with osteoarthritis. BUN, potassium and phosphorus values were elevated post study. Novartis noted that these changes in clinical pathology values were not considered clinically significant.

A 6 month Target Animal Safety Study was also performed to evaluate the safety of Deramaxx administered orally on a daily basis for 6 months. Sixty HEALTHY beagles were used. All dogs survived to termination of the study. Conclusions were that: "Deramaxx tablets were clinically well tolerated by dogs when administered at doses up to 10 mg/kg/day for 26 weeks even though, there was a dose-dependent increase in BUN values at doses > 6 mg/kg/day. Focal renal tubular degeneration /regeneration was seen

[3] **http://www.fda.gov/cvm/index/regulatory/w011603na.pdf**

[4] http://www.fda.gov/cvm/efoi/section**2/141-203s021103.pdf**

at doses > 6 mg/kg/day". [5] [6]

On April 23,2003, the FDA again requested that Novartis immediately cease dissemination of all advertising and labeling materials for Deramaxx which contained certain claims or representations. [7] The FDA specifically referred to the following DER submissions by Novartis:

" Your "Dosing Card" submission of September 24, 2002
Your "Sales Aid" submission of October 8, 2002
Your "Sales Aid on CD" submission of October 17, 2002
Your "Direct Mailer" submission of October 23, 2002
Your "Trade Ad" submission of October 25, 2002
Your "Trade Ad" submission of November 7, 2002

It went on to advise Novartis of its receipt of "additional industry complaint letters regarding marketing practices used in promoting the product Deramaxx (deracoxib)." The FDA further advised of its review of "these promotional materials and concluded that they contain false or misleading statements in violation of the Federal Food, Drug and Cosmetic Act (FDCA) and its implementing regulations." In addition, the FDA noted that "the promotional materials contain information that suggests the use of this product for indications that are not provided for in the labeling."

The FDA specifically noted that "These promotional materials present data from in vitro studies (COX-2 selectivity, Cox-1 sparing, IC50 Ratio) in a way that suggests clinical significance when no clinical benefit has been established via substantial evidence"

It also noted that "These promotional materials imply or state that Deramaxx is safer and more effective than other non-steroidal anti-inflammatory drugs". In this regard, the FDA advised, "We are particularly concerned because CVM's objection to this claim was thoroughly discussed with Novartis representatives during application review. Representatives of Novartis agreed with CVM's Office of New Animal Drug Evaluation that there would be no mention of a "different class for COX-2 selective NSAIDs and presently approved NSAIDS." Meeting memos and Minutes were footnoted to highlight these conversations.

The FDA additionally objected to the fact that "These promotional materials contain suggestions that the drug is effective for managing induced synovial inflammation at the 1mg/kg dose". It went on to say, "Your product is approved at 3-4 mg/kg for post-operative pain. Promotion of the product at 1-2 mg/kg for induced synovial inflammation suggest use of the product for osteoarthritis. At the time of dissemination of these promotional materials, we were not aware of substantial evidence or substantial clinical experience to demonstrate such efficacy. This representation was misleading because it suggests a use that has not been established by substantial evidence or substantial clinical experience."

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[5] **http://dil.vetmed.vt.edu/GreenBookUpdates/2003/2003_05.htm**

[6] http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2003/03-9532.htm

[7] **http://www.fda.gov/cvm/index/retulatory/w042303n.pdf**

The FDA also objected to Novartis failure to "communicate the full extent of risk associated with NSAID therapy" in it's promotional materials.

NOT UNTIL December 22, 2003, ELEVEN MONTHS AFTER the FDA's initial request to cease disseminating the violative and promotional pieces, did Novartis re-label its product. Only after marketing the drug under its new application, did Novartis revise it's previously misleading informational material which had been disseminated widely in 2002 and 2003. On December 22, 2003, Novartis issued it's first "Dear Doctor" letter in which it noted that Deramaxx was "our coxib-class nonsteroidal anti-inflammatory drug (NSAID). Novartis went on to talk about the new information that had come to light, and advised that it had updated the package insert to include a section reporting VOLUNTARY post-approval adverse events. [8]

The updated section of the Deramaxx label warned, in decreasing order of frequency, of numerous adverse reactions, namely, Gastrointestinal, Hematological, Hepatic, Neurological/Behavioral/Special sense, Urinary, Cardiovascular/Respiratory, and Dermatological/Immunological reactions. It went on to warn, "In rare situations, death has been reported as an outcome of the adverse events listed above."

Novartis additionally notified Veterinarians that formerly "precautionary" information had been moved to the "Warnings section" of the label, namely:

"Sensitivity to drug-associated adverse events varies with the individual patient. As a class, cyclooxygenase inhibitor NSAIDs may be associated with gastrointestinal and renal toxicity. Patients at greatest risk for NSAID toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Since many NSAIDs posses the potential to produce gastrointestinal ulceration, concomitant use of DERAMAXX tablets with other anti-inflammatory drugs, such as NSAIDS or corticosteroids, should be avoided or closely monitored."

Dosage and administration changes were also provided to the Doctors. "The approved dose for controlling pain and inflammation associated with orthopedic surgery is 3-4 mg/kg/day as a single daily dose, as needed, **not to exceed 7 days**." This change in labeling put a maximum time period during which Deramaxx at post surgical doses. Novartis went on to advise " For control of pain and inflammation associated with osteoarthritis, the approved dose is 1-2 mg/kg/day as a single daily dose as needed."

Recommended Guidelines for Deramaxx use were also provided and include:

1) "Examine all dogs before prescribing any medication, including Deramaxx;
2) Conduct appropriate laboratory tests in dogs that may be at risk including:
    a. senior pets
    b. pets with history of liver disease, inflammatory bowel disease, renal disease or any other chronic condition.
3) Evaluate potential drug interactions in dogs being treated with concurrent medications, especially steroids or other NSAIDS.
4) Observe appropriate washout periods when switching from one NSAID to another or when following corticosteroid use with NSAID therapy. The length of the washout period will vary, depending upon the patient's condition and other drugs involved.
5) Establish baselines and periodically monitor hematology and serum biochemical data in long-term patients.
6) Provide pet owners with the Deramaxx Owner Information Sheet included with each Deramaxx product shipment and share all potential benefits and possible side effects with them before sending them home with Deramaxx. (Note: Veterinarians can order updated veterinary inserts and

[8] **http://www.fda.gov/cvm/index/safety/DDLDeramax122203.pdf**

updated client information sheets free of charge at any time by calling 1-877-PET-LIT-1 and requesting item number DER 030041B for the revised veterinary insert or item number DER030040046B for the revised client information sheet).

7) Advise pet owners to watch for early signs of drug intolerance including vomiting, diarrhea and lack of appetite, and if they see the signs, discontinue use immediately and contact you."

Thus, it was not until December 22, 2003, in the "Dear Doctor" letter, that the veterinary community was notified of the proper classification of this drug and the numerous adverse effects associated with its use. It is unknown at present whether the general public was ever notified of these labeling changes and adverse reactions through television, the same medium that was used to make them aware of this new drug.

Thereafter, and on 11/29/04, the FDA issued a WARNING LETTER to Novartis regarding its compliance with the ADE reporting requirements. [9]

It began, " During the period of January 20 through January 23, 2004, an inspection was conducted at the headquarters of your veterinary pharmaceutical operations in the United States of America (USA), known as Novartis Animal Health US, Inc. (Novartis), which are located at 3200 Northline Avenue, Suite 300 in Greensboro, North Carolina. The inspection disclosed significant deviations from the adverse drug experience (ADE) reporting requirements of Section 512(l) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations (21 CFR), Sections (§§) 510.300 {effective prior to June 30, 2003) and 514.80 (effective on June 30, 2003)".

It further identified:

"The violations include, but are not limited to, the following areas:

1. Problems associated with your reporting practices of ADEs:
Novartis failed to submit timely and accurate information to the FDA regarding serious ADEs associated with the administration of its FDA approved animal drug product Deramaxx™ (Deracoxib), New Animal Drug Application (NADA) 141-203, during its first year of marketing.
An example of this type of deviation is the recording of the date sent to FDA {box 2b of the FDA 1932). Our inspection revealed significant discrepancies between what was written in box 2b of the FDA 1932 and the postmarked date of the submission and/or the date FDA received the submission. Some of Novartis' initial and follow-up ADE reports, including ones involving death, were postmarked and/or received by FDA between 21 and 100 or more days after the date recorded in box 2b of the FDA 1932, indicating that the date recorded in box 2b is incorrect.
Another example is Case # US200302088, which was reported to Novartis on February 19, 2003 (as indicated in box 2a of the FDA 1932). The form indicates that it was sent to FDA on January 9, 2004, over 10 months after it was reported to Novartis. This information should have been reported to FDA in a timely manner, within 15 working days of receipt. Moreover, the report was not received by FDA until January 27, 2004, again indicating that the date recorded in box 2b was incorrect.
A third example is the revised submission for Case # US200207030, which was submitted with your response dated February 25, 2004. Our investigators reviewed the entire correspondence file between the owner of this animal and Novartis. The FDA 1932 submitted with your response fails

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[9] **http://www.kentuckypetgazette.com/novartis.htm**
Also, **http://www.fda.gov/foi/warning_letters/g5108d.htm**

to include specific details regarding the results of blood work performed on this dog on September 9, 2002 (a baseline) and further work performed in October 2002 and November 2002, which was transmitted to Novartis by the owner between November 2002 and January 2003, in violation of 21 CFR § 514.80(b)(2)(ii). This information should have been promptly reported to FDA within 15 working days of receipt.

Your written response dated February 25, 2004, included revised standard operating procedures (SOPs), which were supposed to address the observed deficiencies. The revised SOP 5.2 (Volume 1, page 650) does not identify how your firm will prevent incorrect information from being reported to FDA as was noted during the inspection.

Your written response dated April 23, 2004, indicates that Novartis has employed additional personnel for the receipt, investigation, and transmittal of ADE reports. The response further states that your firm has also involved corporate quality, compliance, and pharmacovigilance groups to assist in this process. But following your response FDA has continued to receive late ADE reports along with cover letters. For example, some of these letters were dated April 28, 2004; May 12, 2004; May 28, 2004; July 29, 2004; August 20, 2004; and September 21, 2004.

Problems associated with your reporting practices of ADEs related to experimental studies:

Your firm failed to submit timely information to the FDA regarding post-approval studies involving new animal drugs. Two specific failures were identified during the inspection.

The first one was the failure to submit information from completed pilot studies as part of the clinical experience in the annual Drug Experience Report (DER), as required by 21 CFR § 510.300(a)(1) (effective prior to June 30, 2003 and 514.80(b)(4)(iii) (effective on June 30, 2003). Our investigators identified over pilot studies in your master study list. Dr. Tebbit stated that Novartis has never submitted information about their pilot studies as part of the annual DER, unless they are part of an Investigational New Animal Drug Application (INADA) or a pivotal study.

The second one was the failure to submit serious, unexpected ADEs involving animals under study to the FDA within 15 working days of first receiving the information, as required by 21 CFR § 510.300(b)(2)(I) (effective prior to June 30, 2003) and 514.80(b)(2)(I) (effective on June 30, 2003).

One study involving Deramaxx™ (Deracoxib), NADA 141-203, in cats involved a late submission of ADEs. The experiment, which was completed in July 2003, involved 14 animal deaths and other serious ADEs. These ADEs were not reported to the FDA within the required 15 working days time frame, but were reported only after the conclusion of the inspection of your facility, on February 24, 2004.

Although your submission dated February 24,2004, indicates that it was Novartis' intent to disclose the safety information from the cat study, your firm failed to disclose this information from other studies found in the master study List.

For example, a protocol entitled "The Acute Safety Study of an Injectable Deracoxib (SD-6746) Formulation In Dogs" was submitted to the FDA under the INADA 010-865 on April 15, 2002. This was approximately three months after the master study list indicates the pilot study was completed. The study clinical data was not received by the FDA until October 2004.

FDA acknowledges that your firm has revised its SOPS and obtained principal investigator agreements to submit all 15-day ADEs in post approval studies as drug experiences. But your response does not clarify that you also understand that you must submit ADEs in the periodic drug experience report as clinical data, unless they were previously reported, as required by 21 CFR § 514.80(b)(4)(iv)©)."

The FDA went on to advise:

"The specific violations noted in this letter are serious and may be symptomatic of serious

underlying problems.

1. You should take prompt action to correct these deficiencies. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions may include, but are not limited to, seizure and/or injunction. Federal agencies are advised of all Warning Letters about drugs so they may take this information into account when considering the award of contracts.

We request that you reply in writing within fifteen (15) working days of receipt of this letter describing the corrective actions you have implemented, or are planning to implement, to prevent a recurrence of the violations noted above. Please include copies of any available documentation demonstrating that corrections have been made. If corrective actions cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the conditions will be completed."

Thereafter, and on December 1, 2004, Novartis issued another "Dear Colleagues" letter in which the DERAMAXX Update: Clinical Experience with DERAMAXX was provided. This update contained a "summary and analysis of the adverse drug experiences (ADEs) reported to the FDA during the first 18 months of DERAMAXX use."

Novartis further stated that "review and analysis of these data have shown that six of 10 reported ADEs in canine osteoarthritis resulted in unintentional overdose". It went on to urge prescription of this drug "according to recommended guidelines for dosing, patient selection and product administration" and stressed the two different dosing regimens for DERAMAXX.

Please note, this update, was based on 1680 Adverse Drug Events (ADEs) As of January, 3, 2005, ADEs numbered 2400, thus a discrepancy exists in the present number of reported ADEs and those at the time of publication of this Novartis document. This update additionally fails to consider the ADE violations noted by the FDA in it's November 29, 2004 warning letter to Novartis, just 2 days prior to the issuance of this update.

The foregoing chronology is submitted to reveal the story of Deramaxx through the eyes of a pet owners across the country. Documentation of the human-animal bond and the positive effects on human health and well-being of animal companionship is extensive, and at this time, statistics reveal that the overwhelming majority of owners consider their pets as members of their family. This chronology, the facts of which were deciphered from Freedom of Information material and other internet material, reveals extremely minimal testing for a veterinary drug to enter the market, blatant disregard by the drug manufacturer to represent the product accurately in its informational material, and numerous warnings and violations issued by the FDA to the drug manufacturer without any apparent immediate compliance. Per the chronology above, it took Novartis 11 months to re-label it's product as originally approved by the FDA, yet during this 11 month period, it expanded the market for this product by obtaining approval for it's use for the control of pain and inflammation of osteoarthritis. Furthermore, Novartis has failed to timely file ADE's with the FDA.

Additionally, when one considers underreporting of Adverse Drug Events, namely, that the FDA receives by direct report less than 1% of suspected serious ADE, the concern of the pet owner is magnified. [10]

[10] **http://www.fda.gov/medwatch/articles/medcont/postrep.htm#lssrd**

As of January 3, 2005, the FDA reported the following information

Deracoxib - Oral Dog
Reviews: 2352
Treated: 2400
Reacted: 2371
Died: 515 [11]

If underreporting has occurred as estimated, then deaths following the administration of this drug are actually closer to 51,000 in number. Additionally, 515 deaths as of January 1, 2003 represents a 21% mortality rate. This corresponds roughly with the 20.7% death and euthanasia (secondary to side effects) rate published by Novartis in it's December 1, 2004 letter to "Colleagues".

THE PRESENT SITUATION

Animals, specifically dogs, have become central parts of our lives to the extent that they are cared about as if children to millions of people, and valued beyond all monetary considerations. Technology and medicine are advancing at rapid rates, resulting in the proliferation of an ever increasing number of drugs available for both humans and animals. Drug companies are motivated by profit margins. Their reason for existence is to sell the greatest amount of drugs possible and maximize their earnings.

In human medicine, there is (at least theoretically) a value placed on human life more relatively proportionate to its actual value to others. In veterinary medicine, this is not the case, as animals are still legally *property* and thus considered worth, at maximum, purchase or replacement value, which is an infinitesimal fraction of their actual value to owners. (Note recent work on creating new class of property *sentient property* for this/related reasons). Physicians are consequently held to a higher level of liability for malpractice. In addition, and IMPORTANTLY, there exists the *intermediary* of the pharmacist involved in dispensing of medication to humans, which position oversees the safety of each prescription for the individual patient.

In veterinary medicine, there is no intermediary position of "pharmacist". THE VETERINARIAN IS THE PHARMACIST, leaving millions upon millions of animal owners IN the sole hands of their veterinarian, with drug companies and the FDA/federal government purportedly behind them, each and every time medication is dispensed to them. Dispensing drugs for animals is akin to dispensing them for children: in both cases the patient cannot speak for themselves, evaluate the drug, or even report side effects as they occur. Therefore, extra precautions are prerequisite and essential when dispensing medications to either children or animals.

The points above have tragically resulted in a situation today that has genuinely reached crisis proportions: Tens of thousands of animals are being unnecessarily killed each year by side effects of drugs dispensed to them by veterinarians. They are dying unnecessary deaths which could have been, and CAN BE prevented, leaving legions of grief-stricken owners with no notion of how to cope with the death of their beloved animal friend in which they themselves unknowingly participated.

INFORMED CONSENT

January 15, 2004 Emerging issues regarding informed consent

[11] http://www.fda.gov/cvm/index/ade/ade_cum.htm

“The staff at the Food and Drug Administration's Center for Veterinary Medicine has conducted a two-year review of consumer messages to our adverse drug experience hotline. The review indicates increasing concern by consumers about risk and benefit of commonly prescribed, approved animal drugs.

The CVM established the hotline, (888) FDA-VETS, in 1996 to receive calls about adverse experiences to approved animal drugs. We expected many of these reports to come from practicing veterinarians, but our review indicates that a majority of the calls in the past few years have come from consumers, particularly dog owners who find our link on the Internet.

The CVM considers the drug label the first source of important facts for veterinarians. The label is the result of considerable scientific regulatory review before CVM approves the drug. It represents known safety and efficacy for any one drug. The label also gives veterinarians important information about whether the drug is suitable for the individual or subgroup within a species of animal.

Additionally, whenever manufacturers distribute a client information sheet, this means that either the manufacturer or the CVM wishes to convey more facts about safety or efficacy in lay terms to pet owners.

The staff at CVM monitors and evaluates adverse drug experience reports and complaints of inefficacy for approved and unapproved, marketed products. For approved products, this evaluation of postmarket safety and efficacy incorporates knowledge gained from the premarket studies as well as from scrutiny of peer-reviewed studies related to the drug, or the disease that the drug is intended to cure or prevent.

From the hotline, we have learned that pet owners increasingly rely on Internet sources for information when their pets have problems. They have told us that, during their Internet searches, they often find label information and client information sheets.

Frequent comments from pet owners who contact the CVM hotline include these:

* They did not receive a client information sheet when one was available for a drug that was prescribed for their pet.

* The medication they received from their veterinarian was not dispensed in the CVM-approved container but was broken into aliquots that were taken home without the client information sheet or approved label.

* The veterinarian did not conduct or recommend blood testing before and after prescribing the drug, even though baseline testing and/or periodic monitoring was recommended on the label. Common examples include heartworm products and nonsteroidal, anti-inflammatory drugs.

* After reading client information sheets and labels on the Internet about a drug prescribed for their pet, they discovered that their pet may have fallen into a category of animal for which a precaution or contraindication existed.”

These comments represent a complete breakdown and failure of the institution of veterinary medicine. It also represents an unacceptable failure of federal government medical safety oversight programs.

Dr. Victoria Hampshire, author of this article, went on to say:

“Given these findings, we have the following reminders for practitioners:

* Drugs that come with client information sheets are intended to be dispensed in the manufacturer's container, with the sheets accompanying the prescription.

* Product precautions, contraindications, safety information, and warnings should help identify animal patients that are not good candidates for the medication.

* Labels change? if you have a large inventory of a product with a long shelf life, you may want to contact the manufacturer or CVM to obtain the most recent label. A long shelf life makes it likely that some of the product won't be dispensed in the near future. Often, this information is also posted on pharmaceutical companies' official Web sites." [12]

Dr. Hampshire's "reminders" should be pursued as mandates for all veterinary practitioners.

Additionally, the FDA news Drug Daily Bulletin, Thursday, Jan, 27, 2005, Vol. 2, No. 19 states:

"Public Confidence in Drug Companies Declining, Poll Shows

The mounting safety concerns swirling around the pharmaceutical industry are beginning to have a profound effect on the American public's perception of drug companies, according to a recent online poll.

Sixty percent of U.S. adults are "not very confident" or "not confident at all" that drugmakers will publicly disclose information about possible side effects of their products as soon as they have that data, according to a new Harris Interactive survey, which polled 2,404 U.S. adults between Jan. 4 and Jan. 7. Only 5 percent of the survey respondents indicated they are "very confident" that drugmakers will publicly disclose side-effect information in a timely manner....." -Drug Industry Daily [13]

GENERAL OVERVIEW OF PROPOSED SOLUTIONS:

1. The FDA must hold the drug companies responsible for performing thorough safety studies and reporting results accurately and thoroughly for all new veterinary drugs. Omission, manipulation and distortion of data must be curtailed. Close monitoring of all related activities is necessary. Compliance failures must be dealt with swiftly and forcefully in "real time". "Real time" ADE reporting is a critical and essential component of the monitoring the efficacy and safety of new veterinary drugs. An overhaul and upgrade of the ADE reporting system is essential to make the information contained therein easily accessible to the public.

2. Drug companies MUST provide timely, accurate FDA-approved product literature and updates to veterinarians. These materials must contain clear statements that a Client Information Sheet *must* be provided to every client to whom the "new" drug is dispensed.

How Items 1 and 2 can be accomplished :

A. Strong citizen input to FDA demanding:

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[12] http://www.avma.org/onlnews/javma/jan04/040115f.asp

[13] **http://www.fdanews.com/dailies/drugdaily/2_19/news/35001-1.html**

1. Better ADE reporting in “real time”

2. Swift enforcement of labeling violations

3. Correction of all labeling violations to all media vehicles

4. No direct to consumer advertising or promotion allowed for the first 2 years of new drug approval

5. Citizen review committees - public involvement in the drug approval process

B. Pet owners who have been affected by this drug should consult with attorneys regarding:

1. Individual lawsuits

a. “property” claims;

b. claims with respect to failure to obtain client information sheets and lack of informed consent that can be backed by state pharmacy regulations to the extent that vets are not exempt from them.

c. “patient” claims by the “guardian” of the pet

d. “sentient property” claims

e. “Deceptive trade practices” claims

f. “Mail fraud” claims

2. Class Action lawsuits

C. Inform and Advise Legislators of these problems

D. National media campaign raising awareness and support for the above

3. Veterinarians MUST be REQUIRED to provide:

A. A Client Information Sheet (CIS) to every client to whom the drug is dispensed; and

B. Verbal client education regarding potential side effects, and what to do if any are observed in their pet.

4. Veterinarians must be held to similar standards as pharmacists for every medication they dispense to a patient.

How Items 3 and 4 can be accomplished:

A. Influence and Petition American Association of State Veterinary Boards to call for all State Veterinary Board regulations to mandate this (leaving veterinarians unsupported in lawsuits for failure to do so).

B. Make direct appeal to AVMA to call for State Boards to mandate this.

C. Make direct appeals to/demands for individual State Boards to mandate this

D. National “Educate Your Vet” campaign- “VIS*s (Veterinary Information Sheets) designed for clients to give to their vets- “Dear Dr.” letter respectfully, supportively indicating clients can no longer accept less than full information/disclosure w/ drugs.

E. Mass petitions (includes some of above).

Filing with the State Veterinary Board may well be easier and more effective than filing Malpractice claims. Challenging a veterinarian on lack of informed consent and failure to provide Client Information Sheets may prove more productive. Each pet owner should consider each of these alternatives individually and in accordance with their respective state laws.

SPECIFIC SOLUTIONS FOR THE FDA REGARDING NSAIDS IN GENERAL AND DERAMAXX IN PARTICULAR:

1. PACKAGING AND LABELING - ALL NSAIDS - FDA MANDATE THAT NSAIDS BE DISPENSED IN APPROVED CONTAINERS ONLY FOR THE FIRST 1-2 YEARS AFTER PRODUCT APPROVAL

Given the data heretofore mentioned which indicates: that veterinarians operate at the pharmacist level when dispensing drugs: that clients rarely, if ever, receive Client Information Sheets provided by the drug companies to the veterinarian; that veterinarians often and in usual practice purchase drugs in bulk and repackage them for client use; and that the FDA has no direct jurisdiction over vets who are regulated by State Veterinary Boards, it is recommended that NSAIDS be dispensed in approved and appropriately labeled containers only.

BLACK BOX WARNINGS - The most critical warnings that should be black boxed are:

A.) PROVIDE THE CLIENT INFORMATION SHEET - Early treatment of a problem is critical to successful treatment

B.) Provide a profile of the signs associated with typical severe reaction: low RBC, high WBC, High BUN and creatinine, elevated liver values with clinical signs being diarrhea and vomiting, likely with blood and inappetance. This black box warning could be limited to the typical profile that probably accounts for 95% of all severe reaction cases.

There are certainly other signs that come up, but generally, these are either not likely to result in a severe reaction, related to some obvious pre-existing condition (known renal failure, hepatic or cardio impairment as an example), or are relatively rare, i.e., everything is relatively normal, but signs of congestive heart failure.

DOSAGE - With any NSAID, the name of the game is finding the LOWEST POSSIBLE EFFECTIVE DOSE. It should be emphasized that dosing should be at the low end of the range and the pill given on an “as needed” as opposed to “daily” basis

2. ADE REPORTING

Besides upgrading ADE reporting to “real time” and swiftly and appropriately penalizing manufacturers for the failure to comply, the current system of ADE reporting only encompasses unscored data. Scored data regarding death and euthanasia associated with adverse reaction is not made available. The FDA and manufacturers discount the publicly available data, yet the FDA

has the scored data. The public shouldn't have to file FOIA requests to get it.

3. **NO DIRECT TO CONSUMER ADVERTISING OR PROMOTION FOR THE FIRST ONE-TWO YEARS**

This is being advocated for the human drugs. It is equally applicable to veterinary drugs. Pet owners would be better served if manufacturers spend their advertising dollars on further research into the safety and efficacy of these drugs and better "real-time" ADE reporting for the first few years.

4. **PUBLIC INVOLVEMENT IN THE APPROVAL PROCESS**

At present, a drug obtains FDA approval without any opportunity for the public to comment on the safety and efficacy studies. There is no real mechanism for the public to comment on this after approval status is obtained. The FDA needs to change this to allow in the final stages for a public panel to review and comment on the adequacy of the research done in support of a new drug application.

5. **DERAMAXX - PROBLEMS REQUIRING FURTHER INVESTIGATION (AND SUSPENDED SHIPMENT UNTIL THE ISSUES ARE RESOLVED)**

a.) **NSAID HEART problems**. There is enough evidence and details of one well documented case being submitted to the FDA to warrant a requirement that Novartis investigate adverse cardiac effects of Deramaxx. At present, in a question and answer format, Novartis is currently stating that dogs are different than humans and this is not an issue. The fact which undermines this assertion is that dogs are and have been used extensively in studying toxicity and other issues in the development of human Cox-2 inhibitors for humans. Cardio infarcts do not resolve and there is little room for compensation. Most will tend to get worse over time because they are subject to constant blood flows.

b.) **NEUROLOGICAL effects from long-term use.** It is known that Cox-2 is used constitutively in the brain therefore Cox-2 inhibition has to have an effect. What is it? Is it permanent? This needs to be studied.

c.) **SULFA allergy effects**. Deramaxx is a sulfanomide drug. There are certain breeds (Dobermans, white-coated northern and so on) with known sulfa allergies. A specific warning on this needs to be studied. At present, the label says it might be an issue.

d.) **VARIABLE METABOLISM effects**. The studies in support of Deramaxx found that there was variable metabolism of the drug. There is an extensive body of literature on variations in the metabolism of Celebrex, a close chemical cousin of Deramaxx, in dogs. The product label states that there was variation, but does not go beyond this to say that it could result in the death of some dogs. The manufacturers of Deramaxx and other NSAIDS need to develop a screening procedure that identifies slow metabolizers, the dogs who are most likely to experience adverse reactions.

Searle, the developer of Deramaxx, studied this issue when they developed the drug. That information needs to be made public and if it is inadequate to draw any conclusions, studied further since it is clear that this is the reason for most of the severest reactions to the drug. Deramaxx is specifically marketed for osteoarthritis, a condition experienced by older or senior dogs. It is this same group of senior dogs that are normally, the slower metabolizers.

e.) **REVERSIBILITY OF TOXIC EFFECTS** - Because documented adverse side effects of Deramaxx include serious and sometimes fatal organ system damage or failure, the issue of reversibility is a crucial one in order to substantiate claims of safety . It needs to be addressed

scientifically and much more adequately than has been done. If organ system damage is only partially or slightly reversible, the dog might not die right then, however, it's life is still harmed or shortened.

In this same regard, the FDA should consider providing treatment guidelines for Deramaxx drug toxicity, especially given Novartis claims of ineffective treatment and drug overdose events.

Regarding the documentation of the extent of damage done by this drug, the FDA has an up close and personal view day in and day out with benefit of the full clinical record. The FDA should compel the manufacturer to present a "profile" when post-market experience indicates there are serious side effects.

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