TEXAS RACING COMMISSION

P. O. Box 12080 ★ Austin, TX 78711-2080
8505 Cross Park ★ Austin, TX 78754-4552
(512) 833-6699 ★ Fax (512) 833-6907

SAFETY AND MEDICATION WORKING GROUP

Tuesday, October 26, 2010
10:30 a.m.

Texas Veterinary Medical Diagnostic Laboratory
Conference Room
#1 Sippel Road
College Station, Texas 77843
(See parking information below)

Agenda

The Safety and Medication Working Group will meet at the Texas Veterinary Medical Diagnostic Laboratory in College Station to discuss the following items.

I. The importance of protecting the welfare of the racehorse - Jim Heird, Ph.D., Texas A&M University

II. Potential change to the maximum permissible phenylbutazone concentration levels in racehorses

III. Potential changes to the Bleeders and Furosemide Program

   a. Establishment of minimum and maximum dosage levels for furosemide

   b. Request by TQHA to amend provisions relating to horses voluntarily admitted to the Bleeders and Furosemide Program

IV. Update on critical tick disease control and possible policy proposals – Equine Piroplasmosis

Following the meeting, Texas Veterinary Medical Diagnostic Laboratory staff will lead the Working Group on a tour of the Drug Testing Laboratory.

PARKING DIRECTIONS - PLEASE READ - YOU MUST OBTAIN A PARKING HANG TAG FROM TVMDL TO DISPLAY ON YOUR VEHICLE

Turn northwest onto Agronomy Road off Raymond Stotzer Parkway, also known as University Drive and FM 60. This will be a right if you are coming south on Raymond Stotzer, or a left if you are coming north on Raymond Stotzer. Go about 200 feet on Agronomy Road and turn left at first opportunity into parking lot. Follow the driveway through the parking lot until it T's and then turn right. The TVMDL building will be on

your right and you will see parking spaces and signs for "Specimen Drop Off Area." IMPORTANT - You must get a PARKING HANG TAG from the personnel in the TVMDL Front Desk Area. You may either park and then get the hang tag or you may stop and get the tag and then find a parking space. Just make sure you get and display the tag. School is in session and the parking lots are monitored. Once parked, enter the TVMDL building, sign in at the desk, and you will be escorted to the conference room on the second floor.

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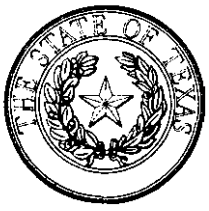

SAFETY AND MEDICATION WORKING GROUP

Tuesday, October 26, 2010
10:30 a.m.

Texas Veterinary Medical Diagnostic Laboratory
Conference Room #1 Sippel Road
College Station, Texas 77843

Order of Discussion

I. Call to Order and Remarks by Working Group Chair Kent Carter, DVM

II. Introductions

III. Presentations and Discussion

A. Jim Heird, Ph.D., Executive Professor and Coordinator of the Equine Initiative at Texas A&M University, will discuss the importance of protecting the welfare of the horse.

B. Dr. Ken Quirk, Chief Veterinarian, will lead a discussion on a proposed change to the allowable phenylbutazone threshold in a horse from 5.0 micrograms to 2.0 micrograms. RCI adopted this change to its model rule, as recommended by the RCI Regulatory Veterinarians Committee.

C. Discussion of elements of the Bleeders and Furosemide Program

Dr. Quirk will lead a discussion on whether the Commission should require a minimum dosage of furosemide be given to those horses in the Bleeders Program. RCI model rule states the dosage shall not exceed 500 mg. nor be less than 150 mg.

Rob Werstler, Texas Quarter Horse Association, will present his request to amend the Bleeders and Furosemide Program. The proposed change affects only those horses that a trainer has voluntarily admitted to the program.

D. Dr. Quirk will provide an update on Equine Piroplasmosis, including the current entry requirements at Texas racetracks, and lead a discussion on whether the Commission should require testing for EP by rule.

Following the meeting, Texas Veterinary Medical Diagnostic Laboratory staff will lead the Working Group on a tour of the Drug Testing Laboratory.

ITEM II.

POTENTIAL CHANGES TO THE MAXIMUM PERMISSIBLE PHENYLBUTAZONE CONCENTRATION LEVELS IN RACEHORSES

1. Texas Rules of Racing
Section 319.3 Medication Restricted,
Page 1

2. Press Releases
RCI Model Rules Committee
Recommends Pulling Back on Bute &
RCI Lowers Bute Threshold,
Pages 2-6

3. "The Use of Phenylbutazone in the Horse" by
Lawrence R. Soma, VMD,
University of Pennsylvania,
Prepared at the request of the Racing Medication
and Testing Consortium,
Pages 7-31

TEXAS RACING COMMISSION
RULES OF RACING
Sec. 319.3. Medication Restricted.

Sec. 319.3. Medication Restricted.
(a) Except as otherwise provided by this section, a horse or greyhound participating in a race may not carry in its body a prohibited drug, chemical, or other substance.
(b) The maximum permissible plasma or serum concentration of phenylbutazone in horses is 5.0 micrograms per milliliter.
(c) Furosemide at or below the approved tolerance level in a horse that has been admitted to the furosemide program is permissible. The approved tolerance level shall be published on the list of therapeutic drugs posted under subsection (d) of this section.
(d) Trace levels of drugs which are therapeutic and necessary for treatment of illness or injury in race animals are permissible, provided:
(1) the therapeutic drug is on a written list approved by the executive secretary, maintained by the commission veterinarian, and posted in the commission veterinarians' office; and
(2) the maximum permissible urine or blood concentration of the drug does not exceed the published limit, if any, on the written list of therapeutic drugs.
(e) Except as otherwise provided by this chapter, a person may not administer or cause to be administered to a horse or greyhound a prohibited drug, chemical, or other substance, by injection, by oral or topical administration, by rectal infusion or suppository, by nasogastric intubation, or by inhalation, and any other means during the 24-hour period before the post time for the race in which the animal is entered.
(f) A positive finding by a chemist of a prohibited drug, chemical, or other substance in a test specimen of a horse or greyhound collected before or after the running of a race, subject to the rules of the commission relating to split specimens, is prima facie evidence that the prohibited drug, chemical, or other substance was administered to the animal and was carried in the body of the animal while participating in a race.
(Added eff. 8/14/89; (a), (f), (g) amended eff. 11/29/90; (h) added eff. 11/29/90; (b) amended 4/3/91; (h) deleted eff. 11/22/91; (d), (f) amended eff. 8/3/92; amended eff. 11/1/98; (c) amended eff. 11/1/01)

RACING COMMISSIONERS INTERNATIONAL

Press Release

Contact: Ed Martin 859-224-7070
Friday, October 22, 2010

RCI Lowers Bute Threshold

LEXINGTON, Ky. – In an effort to improve the pre-race examinations of racehorse, the Board of Directors of the Association of Racing Commissioners International (RCI) gave final approval today to lower the allowable level of phenylbutazone

The board voted 16-0 in favor of lowering the threshold for penalty from 5 micrograms of phenylbutazone (bute) per milliliter of plasma or serum to 2 micrograms, paving the way to improved pre-race examinations conducted by regulatory veterinarians.

RCI President Ed Martin said "Absent a compelling and convincing medical reason to the contrary, the RCI has concluded that it is in the interest of the horse that the proposed change be adopted." He noted that RCI will now review the current penalty guidelines to address concerns that have been raised pertaining to potential first-time violations of the new rule. RCI's Model Rules Committee, in supporting the change, recommended that jurisdictions work with local horseman's groups to transition to the new policy and consider a grace period so trainers can adjust.

The change to the Model Rule comes after months of research and discussion, beginning with the RCI Regulatory Veterinarian Committee, who voiced concerns that phenylbutazone could interfere with pre-race examinations due to the possibility of analgesic effects of the drug. RCI asked the Racing and Medication Testing Consortium (RMTC) to review the research on the topic, and the Scientific Advisory Committee of the RMTC voted without objection to support the lowering of the threshold.

The RCI Model Rules Committee had planned to vote on the matter during a spring meeting, but at the request of the National Horsemen's Benevolent and Protective Association (HBPA) delayed that vote until after the topic could be discussed at their Annual Meeting.

After considering alternate viewpoints expressed at the National HBPA meeting, the RCI Model Rules Committee voted in favor of lowering the threshold in September. The lowered threshold received formal support from groups such as the American Association of Equine Practitioners, The Jockey Club, The Jockeys' Guild, and the Thoroughbred Owners and Breeders Association.

Because the proposed new racing regulatory compact is not yet in existence, the adoption of the model rule change will occur in different jurisdictions at different times, as individual commissions commence formal rule making on an individual basis.

1510 Newtown Pike, Lexington, Kentucky 40511
859-224-7070

In related news, the RCI Board of Directors voted 11-1 (4 abstentions) in favor of a change to the Model Rules dealing with fees paid to jockeys of Thoroughbred, Quarter Horse, and other flat races. The new rule clarifies when jockey fees are earned by riders, and specifically deals with situations when changes are made to the rider of a horse by an owner, trainer, or the jockey.

For a copy of the RCI Model Rules, please visit http://www.arci.com and click the link RCI Model Rules.

RACING COMMISSIONERS INTERNATIONAL

Press Release

Friday, September 16, 2010

Contact: Ed Martin 859-224-7070
www.arci.com

RCI Model Rules Committee Recommends Pulling Back on Bute

LEXINGTON, Ky. - The Association of Racing Commissioners International (RCI) Model Rules Committee voted unanimously today to recommend lowering the threshold of the non-steroidal anti-inflammatory drug phenylbutazone.

The committee acted on recommendations from the RCI Regulatory Veterinarians Committee, the RCI Drug Testing Standards and Practices Committee, the Racing Medication and Testing Consortium, the Jockey Club's Thoroughbred Safety Committee, the Jockey's Guild, the Thoroughbred Owners and Breeders Association and the American Association of Equine Practitioners.

The model rule change was not without controversy as the National HBPA, the Thoroughbred Owners of California, and the California Thoroughbred Trainers submitted statements urging RCI not to approve the proposal. Some proposed additional research.

The proposed change will result in a lowered allowance of 2 micrograms of phenylbutazone per milliliter of plasma or serum, down from 5 micrograms as currently stated in the RCI Model Rules.

The lowered threshold is not a new idea as Maryland and Pennsylvania currently have the 2 microgram threshold in place.

Although the decision by the Model Rules Committee is a major step towards a lower threshold, the change will not be fully adopted as a Model Rule until it is approved by the RCI Board of Directors, which is expected to convene in early October.

For a link to the ARCI Model Rules, please visit the RCI website at www.arci.com.

Please see the attached Statement by RCI President Ed Martin.

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Statement of:
Edward Martin, President
Association of Racing Commissioners International.

The RCI Model Rules Committee has received valuable input on the proposed rule change lowering the allowed threshold of phenylbutazone from 5 micrograms per milliliter serum or plasma to 2 micrograms per milliliter serum or plasma. We sincerely thank all individuals and organizations that have submitted information to us. That information has been reviewed and considered and we appreciate those who have taken the time to research this matter, particularly Dr Shields, Dr. Soma, The National HBPA, The Jockey Club's Health and Welfare Committee, the Scientific Advisory Committee of the Racing Medication and Testing Consortium, and the American Association of Equine Practitioners. We also thank the Jockeys Guild, the Thoroughbred Owners and Breeders Association, Thoroughbred Owners of California, and California Thoroughbred Trainers.

It is clear that a debate exists on the science. The scientific review process within the Racing Medication and Testing Consortium was developed to address such matters. It is unfortunate and troubling that some now question the thoroughness of that review. The RMTC process is necessary to ensure that the omnipresent scientific debate is structured so regulators, horsemen, owners, and fans can understand and rely on recommendations that reflect the preponderant scientific view, if not a consensus, of the best advisors we have at our disposal.

RCI, on the recommendation of the Regulatory Veterinarians Committee, requested the RMTC conduct a review of the use of non-steroidal anti-inflammatory medications. The committee members expressed a concern that current recommended policy may jeopardize the integrity of pre-race equine examinations. We appreciate the willingness of the RMTC to commit resources to this review as well as the review we have requested pertaining to the use of corticosteroids.

At no point during the Model Rules Committee's deliberate review process did opponents of this policy change present an argument as to why the administration of phenylbutazone close enough to race time to trigger a 5 microgram threshold was absolutely necessary to the health of the horse. The unanswered question by those in opposition to the proposed policy change is why a horse in pain requiring an administration of phenylbutazone at their suggested level should be racing.

Phenylbutazone treats muscular sprains, tendonitis, acute joint injury, and arthritic conditions. There are clear warnings that's its overuse could seriously jeopardize equine health. The misuse of of this drug may be hurtful to our horses, causing ulcers or hemorrhages in the esophagus and gastrointestinal tract, diarrhea, low white blood cell count, anemia, and intestinal, kidney, and liver disease.

Because our horses cannot speak, we believe there is no other choice but to be cautious. Even if we were to agree - and we are not - with those who claim that the process by which the science was assessed was flawed, the prudent course for public policy makers would be to err on the side of caution in the interest of the horse and rider.

Absent a compelling and convincing medical reason to the contrary, the RCI Model Rules committee has concluded that it is in the interest of the horse that the proposed change be adopted. The committee approved this change primarily to address the concerns raised by the regulatory veterinarians.

We believe the administration of any medication should be determined by a licensed veterinarian acting in the best interest of the horse. The fact that the American Association of Equine Practitioners is supportive of the proposed change speaks volumes as to the merit of the proposal.

Concerns have been expressed that some horsemen may have become overly reliant on NSAIDs. If this is so we question the extent to which such over reliance may contribute to the high level of gastronic ulcers in racehorses. We question the extent that the chronic use of phenylbutazone in horses with joint problems might be causing more problems than it's preventing. We question whether attention is being paid to the strong recommendation from researchers at Louisiana State University that hematologic (blood) tests be conducted as early as three to five days after initiating treatment with phenylbutazone. We question whether those who rely on phenylbutazone as part of a horses's normal training regime are aware that the National Toxicology Program has identified this drug as a potential carcinogen.

The Model Rules Committee recommends that implementation of this change by racing commissions should be done in consultation with the horsemen and we encourage commissions to deploy a transition or grace period prior to full enforcement of the rule change.

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1510 Newtown Pike, Lexington, Kentucky 40511
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Lawrence R. Soma, VMD,
University of Pennsylvania,
School of Veterinary Medicine.

This review was undertaken at the request of the Racing Medication and Testing Consortium, Medication Advisory Committee.

Review: The use of phenylbutazone in the horse

This review presents a brief historical prospective of the genesis of regulated medication in the US racing industry of which the non-steroidal anti-inflammatory drug phenylbutazone (PBZ) is the focus. It presents some historical guide posts in the development of the current rules on the use on PBZ by racing jurisdictions in the US. Based on its prevalent use, PBZ still remains a focus of attention. The review examines the information presented in a number of different models used to determine the effects and duration of PBZ in the horse. They include naturally occurring lameness and reversible induced lameness models that directly examine the effects and duration of the administration of various doses of PBZ. The review also examines indirect plasma and tissue models studying the suppression of the release of arachidonic acid-derived mediators of inflammation. The majority of studies suggest an effect of PBZ at 24 hours at 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not perform a pre-purchase lameness examination unless the horse is shown to be free of NSAID. This remains the opinion of many Commission Veterinarians in that they wish to examine a horse pre-race without the possibility of a NSAID interfering with the examination and masking possible musculoskeletal conditions. Based on scientific studies, residual effects of PBZ remain at 24 hours following administration. The impact of sustained effect on the health and welfare of the horse and its contribution to injuries during competition remains problematic.

Historical Prospective

Phenylbutazone (PBZ) is second only to aspirin as one of the oldest non-steroidal anti-inflammatory drugs (NSAID). It was introduced into veterinary medical practice in the 1950s and still remains one of the more commonly used non-steroidal anti-inflammatory drugs in the horse (Tobin, Chay et al., 1986). In 1959 it was approved for use in racing by the State of Colorado and some attribute this ruling as the beginning of the era of controlled medication in racing (Tobin, 1981). Phenylbutazone became news worthy in 1968 when Dancers' Image won the Kentucky Derby and the post-race urine tested positive for PBZ. By the early 1970's it was legalized in most states and became well established by the mid 70's (Gowen & Lengel, 1993). In some racing jurisdictions as long as the sum of the combined urine concentration of PBZ and its metabolite, oxyphenbutazone (OPBZ), did not exceed a prescribed concentration, the horse was not in violation of the medication rules. In 1977 the National Association of State Racing Commissioners Veterinary-Chemist Advisory Committee concluded that "PBZ does not change a horse's innate ability to race, but by relieving inflammation it may enable the horse to race closer to maximum capabilities" (Gabel, Tobin et al., 1977). In the late 1979, the use of PBZ came under scrutiny which resulted in the publication of the book "The Misuse of Drugs in Horse Racing: a Survey of Authoritative Information on Medication of Race Horses" by the Illinois Hooved Humane Society. This publication stirred controversy on the use of PBZ especially on race day and many jurisdictions revised their rules on race day use of PBZ. In 1982 a Committee appointed by the National Association of State Racing Commissions recommended 2μg/ml as the decision or regulatory plasma/serum concentration of PBZ. Thin layer chromatography was the primary method of drug screening in urine at this time. This proposed concentration (2μg/ml) was based on the concerns of racing chemists that high PBZ blood concentrations would produce urinary PBZ and metabolites that would interfere with or "mask" detection of other drugs (Gabel, Tobin et al., 1977). Subsequent to this, further studies indicated that the "masking effect" was not a concern (Woods, Chay et al., 1985; Woods, Chay et al., 1985; Tobin, Chay et al., 1986; Woods, Weckman et al., 1986) and following further review the suggested upper plasma/serum threshold concentration was increased to 5μg/ml. Complete uniformity does not exist among racing jurisdiction many have remained at 2 μg/ml and others are at 5μg/ml, or at some concentration in between.

Clinical opinions on the use of phenylbutazone.

Phenylbutazone is considered valuable in the training of sore horses to maintain fitness in those with early joint or ligament problems. The use of a NSAID such as PBZ enables a horse to continue training or return to training in a shorter period of time. On the other hand a major drawback to the use of PBZ is the veterinarians' inability to evaluate the degree of lameness with this medications present in the horse's system (Cannon, 1973). It was also the opinion of many veterinarians that PBZ would allow a horse to compete with mild chronic arthritic changes, but did not possess sufficient anti-inflammatory activity to allow a horse with a serious injury to compete. Non-steroidal anti-inflammatory drugs can be used to restore normal performance in a horse debilitated by some injury to joints, tendons, or muscle achieved by its anti-inflammatory

actions and relief of pain. The short-term effects are not in doubt, but the long-term merits of continuous administration of PBZ in many cases are problematic. The cynical remark that some therapies, such as corticosteroids and NSAID allow the patient to walk to the post-mortem room is an overstatement but the veterinarian must consider the long-term effect of therapy and that resting the horse maybe the best approach (Sanford, 1983). Many veterinarians consider the use of NSAID justified in show-horses, show-jumpers, and combined training and have presented opinions on the use of PBZ based on the activity of the horse (Dunn, 1972). The United States Equestrian Federation rules allow higher concentration during competition compared to racing industry rules. There is great therapeutic value in the use of PBZ in the treatment of acute inflammatory conditions or in older horses in a non-racing environment for the treatment of chronic osteo-arthritis where it can extent the useful life of the horse (Barragry, 1973).

An ethical and moral dilemma confronts the practicing veterinarian when prescribing PBZ or other medications for the treatment of the varied musculoskeletal condition in competition horses especially race horses; will the medication allow a horse to maintain a training schedule thereby allow the animal to function or is the medication contributing to further injury to the detriment of the horse? This is especially true in younger horses with a fresh injury and an unsuspecting owner administering an NSAID and inflicting further damage. Many veterinarians agree that the use of anti-inflammatory drugs could mask unsoundness in horses being examined in a pre-purchase examination for soundness (Dunn, 1972). Non steroidal anti-inflammatory drugs including PBZ, have masked clinical signs that have resulted in cecal perforation (Ross, Martin et al., 1985). Masking of existing musculoskeletal condition is the concern of Racing Commission Veterinarians who are examining horses on a daily basis knowing that the examination is not in a medication-free horse.

In a multicentre field study, PBZ and suxibuzone, a pro-drug of PBZ, were equally effective in the treatment of a number of acute, chronic, nonspecific lameness in which all horses were consistently lame upon trotting. Approximately 50% of the horses showed an improvement within 3 days of treatment with 30% showing an additional improvement at 6 days (Sabate, Homedes et al., 2009). This study illustrated the concern of many veterinarians as to the duration of administration of PBZ; if significant improvement had not occurred within 4 to 5 days re-evaluation should be performed (Jeffcott & Colles, 1977; Reilly, 2000).

Toxicity of PBZ in the horse and ponies has been reviewed and several factors may predispose towards PBZ toxicity in the horse, including breed and age, but high dose is considered to be particularly important (Lees & Higgins, 1985). Clinical experience suggests that PBZ can be administered to horses in modest doses for a prolonged period of time without detectable side-effects.(Tobin, Chay et al., 1986). Blood dyscrasias commonly described in man have not been reported in the horse and despite the lack of documented evidence, toxicity of PBZ in the horse is considered to be lower than that in human. Phenylbutazone should not be administered if there are signs of gastro-intestinal ulceration, clotting defects or any cardiac, renal or hepatic dysfunction (Jeffcott & Colles, 1977). Despite the apparent lack of toxicity, adverse effects on the gastrointestinal track have been reported when administered at high doses

(Karcher, Dill et al., 1990; Meschter, Gilbert et al., 1990; Meschter, Gilbert et al., 1990). Possible toxic effects of NASID are not limited to PBZ. Multiple daily administration of therapeutic doses of ketoprofen (2.2 mg/kg), flunixin meglumine (1.1 mg/kg), or PBZ (4.4 mg/kg) IV, every 8 hours, for 12 days produced changes in the glandular portion of the stomach which was the area of the gastrointestinal tract most severely affected. Results of CBC, serum biochemical analyses, and fecal occult blood tests were not different from those of control horses with the exception of PBZ-treated horses that had a significant decrease in serum total protein and albumin concentrations. Moderate to severe ulcerative colitis was diagnosed during necropsy, exploratory celiotomy and biopsy; it was concluded that the ulcerative lesions may have gone unreported due to the anti-inflammatory effects of NSAID's (Karcher, Dill et al., 1990). Renal papillary necrosis has been reported in horses to which PBZ was administered (Gunson, 1983) and medullary crest necrosis was reported in horses placed on maintenance doses of PBZ (Read, 1983). Renal crest necrosis has also been reported in horses to which flunixin and PBZ were administered (MacAllister, Morgan et al., 1993). In horses on daily doses of 8.8mg/kg for 21 days plasma albumin concentrations decreased significantly from days 10 to 21, treatment also caused neutropenia. No other clinical or hematologic abnormalities were detected for PBZ or control horses (McConnico, Morgan et al., 2008). A retrospective study of 269 horses administered less than or equal to 8.8 mg/kg/day PBZ for 4 days or the lower dose of 2 to 4 mg/kg of body weight/day for up to 50 days remained clinically normal (Collins & Tyler, 1984).

The current lack of toxicity and observable side-effects was based on the realization that the loading dose (4.4mg/kg twice for 4 days) recommended by the manufacturer could be reduced. A revised schedule of 4.4 mg/kg twice daily for one day followed by 2.2mg/kg twice daily for four days, then 2.2 mg/kg daily or as needed increased the margin of safety as no changes in clinical biochemistry or hematology were observed (Taylor, Walland et al., 1983). This modified dose regimen did not compromise clinical efficiency (Taylor, Verrall et al., 1983). The American Association of Equine Practitioners recommends a dose of 2.2mg/kg daily with the last dose not more than 24 hours prior to post time (Harvey, 1983). Clinical use of PBZ for many years suggests that with adequate care, hydration, and the use of the lower therapeutic doses of PBZ can be used safely without clinically detectable side-effects. The exception is the administration of a combined treatment of PBZ with flunixin to horses as detrimental effects may outweigh any potential benefits. Gastroscopy of 4 horses revealed substantial gastric ulcers when administered the combination NSAID treatment (Reed, Messer et al., 2006).

In the equine, a dose-finding study for PBZ has not been reported, that is the evaluation of the improvement in clinical conditions at various doses. The current dose schedules are based on years of clinical use by many or administered doses to meet regulatory requirements of the industry. Based on the opinions and observations of veterinarians, investigators conducted a number of studies to determine the plasma PBZ concentrations 24 hours following various dosing schedules, formulations, and dosages (Soma, Gallis et al., 1983; Chay, Woods et al., 1984; Houston, Chay et al., 1985; Soma, Sams et al., 1985). Following completion of these

studies, the recommended dosing schedule was as follows: oral administration of 4.4 mg/kg (2 g) for 3-4 days followed by a single IV dose of 4.4mg/kg 24 h prior to racing. If these dosing recommendations were followed, plasma PBZ concentrations on race day should not exceed 5μg/ml. However, these studies did not attempt to determine the pharmacological effect of PBZ at 24 hours or the pharmacological effects of a plasma concentration of 5μg/mL, and this was the major drawback in the study.

A prime consideration in the continuous use of PBZ or other NSAID is the possible contribution to catastrophic and non-catastrophic injuries. In the human sport medicine, which also applies to the veterinary field there is a lack of high-quality evidence to guide practitioners in their use and the possible adverse effects that have clinical relevance. Potential negative consequences on long-term use and the healing process are slowly growing (Fournier, Leal et al., 2008). Specifically, NSAID are not recommended in the treatment of completed fractures, stress fractures or chronic muscle injury. The only exception may be very short-term use for analgesic purposes or as an adjunct to other analgesics. Judicious use of NSAID may be more appropriate in the management of acute muscle and ligament sprains, tendinitis, and muscle injury. However, length of treatment should always be kept as short as possible (Mehallo, Drezner et al., 2006). Cyclooxygenase activity is involved in the healing of many skeletal tissues, either directly or indirectly through modulation of the inflammatory response. Consequently, pharmacological manipulation of cyclooxygenase using NSAID can profoundly affect skeletal health. All of the NSAID should be not be painted with a broad brush as having negative effects on healing and recovery of all types of injuries. In particular, NSAID use does not appear to have a long-term negative effect on tendons and ligaments and NSAID therapy may inhibit adhesion formation during tendon healing, which leads to a better functional recovery (O'Connor, Lysz et al., 2008). There is limited information on the use of PBZ and other NSAID on healing and synovial membrane health in the horse and many of the studies were conducted in-vitro.

Oral administration of PBZ for 14 days significantly decreased proteoglycan synthesis in articular culture explants from healthy horses; these authors suggested that PBZ should be used judiciously in equine athletes with osteoarthritis, because chronic administration may suppress proteoglycan synthesis and potentiate cartilage damage (Beluche, Bertone et al., 2001). It has been suggested that the use of PBZ early in the post operative period may interfere with bone healing (Rohde, Anderson et al., 2000). In horses with experimentally induced osteoarthritis the use of a COX-2 inhibitor, diclofenac, induced significantly less radial carpal bone sclerosis and overall gross cartilage erosion, compared with PBZ. Results obtained suggest that diclofenac had both clinical sign-modifying and disease-modifying effects. Only clinical sign-modifying effects were detected in association with PBZ administration (Frisbie, McIlwraith et al., 2009).

The effects of NSAID, including PBZ, were investigated on lip polysaccharide-challenged and unchallenged equine synovial membrane in terms of production of prostaglandins E_2 (PGE_2) and hyaluronan, viability, and histomorphologic characteristics. These investigators concluded that the commonly used NSAID suppress induced synovial membrane PGE_2 production without detrimental effects on synovial membrane viability and function (Moses,

Hardy et al., 2001). Results of studies have also suggested that hyaluronan and carprofen might exert an anti-arthritic action through stimulation of PG synthesis and there is possible justification for therapeutic administration of enantiomeric rather than racemic carprofen (Frean, Abraham et al., 1999). Others have also suggested that use of carprofen in osteoarthritis horses may induce beneficial changes in articular cartilage matrix (Armstrong & Lees, 1999).

Catastrophic injuries remain an unavoidable but public relations nightmare in the racing industry, despite the fact that injuries in athletic competition are expected. The immediate perception in racing is that the injury is drug-related, when in fact there are many horse-related and external factors that contribute to musculoskeletal injuries. One study did conclude that higher concentrations of PBZ and other NSAID did contribute to a higher incidence of racetrack injury (Dirikolu, Woods et al., 2009). The plasma concentrations of PBZ in this report were higher than are currently allowed in most racing jurisdictions. Racing jurisdictions allow plasma concentrations of PBZ or flunixin; therefore, many horses are competing at plasma concentrations near the allowable limits. About 20% of the plasma samples exceeded 5ug/ml at time of pre-race examination (Arthur, 2009). The question that still remains is what are the long-term effects of the continuous use of NSAID on the musculoskeletal health of the horse? Are the short-term benefits of allowing the horse to compete under the influence of an NSAID worth the long-term risks? The veterinarian does have a greater choice of NSAID than just PBZ for the treatment of osteoarthritis in horses (Goodrich & Nixon, 2006) and it is inevitable that a horse may have to compete on a residual concentration of drug used during training. It may be of benefit to the horse to expand the veterinarian's regimen of allowable residual concentration of a more diverse list of NSAID.

Phenylbutazone and performance.

Results from performance studies suggested that PBZ had no clear effect on the performance of normal, healthy horses (Sanford, 1974). Plasma concentration of prostaglandins were increased in human (Demers, Harrison et al., 1981) and equine during exercise (Birks, Gory et al., 1991; Mitten, Hinchcliff et al., 1995). These exercise-induced increases in cyclooxygenase activity was inhibited by the administration of PBZ, but PBZ did not produce detectable changes in systemic hemodynamic or acid-base variables in either standing or running horses (Hinchcliff, McKeever et al., 1994). In exercising horses, the effect of inhibition of cyclooxygenase activity on the hemodynamic response was examined. Administration of PBZ abolished the exertion-induced increases in plasma 6-ketoprostaglandin F_1 alpha and TXB_2. Phenylbutazone treatment resulted in significantly higher heart rates and right atrial pressures than control. There was no effect of PBZ on carotid or pulmonary arterial pressures, oxygen consumption, carbon dioxide production, blood lactate concentrations, or plasma volume during exertion. These results suggest that cyclooxygenase products likely mediate or modulate some of the systemic hemodynamic responses to exertion in horses (Mitten, Hinchcliff et al., 1996), but there is no evidence that the administration of PBZ and/or the suppression of cyclooxygenase products alters performance. In a similar study, the administration of PBZ (4.4mg/kg) to the horse did not show significant differences from control horses in heart rate, right atrial, and

pulmonary vascular pressures during high speed treadmill studies (Manohar, Goetz et al., 1996). Endurance-like exercise (12km/h for 3 hours) did not affect the kinetic disposition of PBZ and dexamethasone. The conclusion of these authors was that resting horse can be used for determination of pharmacokinetics as no differences were noted in the disposition kinetics and the plasma-concentration time curves for the horse when at rest or sampling during exercise (Authie, Garcia et al., 2010).

Pain perception

Pain experience and expression is difficult to determine in the horse as it is influenced by many factors such as species, breed, individual variations, and environmental characteristics. Equally difficult to assess is the alteration of pain by analgesic drugs. Latency to the onset of flexion of the limb in response to a noxious thermal stimulus and heat-evoked skin twitch have been reliable and reproducible measures of pain threshold and a nociceptive end-point for analgesic studies in the horse (Kamerling, Weckman et al., 1985). Thermal-evoked skin-twitch reflex and thermal evoked hoof withdrawal reflex have been used to compare analgesic activity of procaine, mepivacaine and PBZ. Compared to procaine and mepivacaine, PBZ failed to alter pain thresholds over a 36 hours post-administration (Kamerling, Dequick et al., 1984). This type of stimulation produces an acute pain response and can be objectively used to compare the duration of regionally administered anesthetic agents and other drugs used to reduce the perception of pain. In the horse, PBZ was indistinguishable from saline controls when using a thermal stimulus (Kamerling, DeQuick et al., 1983). Phenylbutazone was not an effective drug when used to block thermal and specific nociceptive pain stimuli. UU

Post-operative pain.

Post-operative pain can be considered primarily a nociceptive pain produced by trauma to tissues due to direct intervention and disruption of these tissues. Inflammation due to surgical trauma is a part of the pain response and the use of NSAID has been promoted for this purpose post-operatively. Minimal differences were noted between PBZ and placebo administrations in a group of horses undergoing arthroscopic surgery (Raekallio, Taylor et al., 1997). In a similar post-operative study, flunixin, PBZ or carprofen was administered intra-operatively just prior to the end of anesthesia. The time following surgery when additional analgesic drugs were required post-operatively were; 8.4 hours, 11.7 hours and 12.8 hours for PBZ, carprofen, and flunixin, respectively. Horses that were administered the opioid, butorphanol, during surgery needed significantly fewer analgesic agents post-operatively (Johnson, Taylor et al., 1993).

In a double-blind, randomized, prospective study of human patients undergoing arthroscopic surgery, those who were administered a prostaglandin inhibitor (naproxen sodium) had significantly less pain, less synovitis, less effusion and faster recovery (Ogilvie-Harris, Bauer et al., 1985; Rasmussen, Thomsen et al., 1993) than those without. In equally as large a prospective study, no advantages were observed over control group of patients when compared to physical therapy and administration of the NSAID diclofenac (Birch, Sly et al., 1993).

The use of NSAID in combination with more potent opioids for high-intensity pain and the weaker opioids for moderate-to low-intensity pain has been the topic of numerous

publications discussing emerging trends in pain management (Schug, Manopas et al., 2007; Fischer, Simanski et al., 2008; Huang, Wang et al., 2008; Layzell & Layzell, 2008). Despite the use of PBZ postoperatively on a routine basis similar studies in the total management of post operative pain using NSAID combined with the opioids are lacking in the equine. The role of NSAID in the management of post-operative pain was suggested in an early publication (Mather, 1992) and authors still suggest they may contribute to improved functional outcomes without significant adverse effects (Reuben & Reuben, 2007).

Central nervous system effects and crossing of the 'blood brain barrier'UU.

Phenylbutazone has no known spinal or central nervous system (CNS) effects that are involved in the suppression of pain. The effects are primarily thought to be peripheral in action without CNS action or any noticeable sedation. To exert a central effect NSAID have to cross the blood-brain barrier. Transfer across the blood-brain barrier is controlled by simple physico-chemical factors. Oxyphenbutazone, indomethacin, ketoprofen are characterized by high lipophilicity. At steady state, their free plasma concentrations correspond to their cerebral spinal fluid concentrations. (Bannwarth, Netter et al., 1989). The presence of these NSAID in the brain may explain the antipyretic properties and some side effects of the NSAID. Concentrations of OPBZ in spinal fluid are similar to corresponding concentrations of unbound free OPBZ in plasma, which is approximately 5% of the total concentration of OPBZ in plasma (Gaucher, Netter et al., 1983). Similarly, cerebral spinal fluid concentrations of ketoprofen reflect the unbound plasma ketoprofen concentrations and were in equilibrium with the plasma concentration from 2 to 13 hours after administration (Netter, Lapicque et al., 1985). Ibuprofen, flurbiprofen, and indomethacin rapidly cross the blood-brain barrier. Plasma protein binding limits the driving force for uptake of NSAID into the brain by reducing the free fraction of NSAID in plasma (Parepally, Mandula et al., 2006). The observation that long-term treatment of patients with ibuprofen results in a reduced risk and delayed onset of Alzheimer's disease suggests that it crosses the blood-brain barrier, has a central effect, and reduces inflammation in the Alzheimer's disease brain (Dokmeci & Dokmeci, 2004). Attempts to correlate the CSF concentrations of indomethacin with its regional inflammatory suppression and analgesic activity have not been successful (Bannwarth, Netter et al., 1989). The assumption that all NSAID relieve pain only through an inhibition of prostaglandins synthesis, have no antinociceptive effects, central effects, and all actions are peripheral in nature have been challenged (McCormack & Brune, 1991).

Concentrations of PBZ in Synovial Fluid

The efficacy of NSAID in joint diseases depends on their concentrations within the joint as the cells within the joint are the major site of action (Furst, 1985). There is no barrier to the diffusion of unbound NSAID into the joint cavity and their therapeutic effectiveness is determined by passage across the synovial membrane which can depend on the degree of inflammation of the joint and on the pharmacokinetic properties of the drugs. Most NSAID are weak acids with a pK_a between 3 and 6 and the un-ionized forms are lipid soluble. The NSAID are primarily in the ionized form as the pK_a values are much lower than the pH of blood. The

proportion changes to un-ionized as the environment becomes more acidic as in the stomach, kidneys and more importantly inflamed tissues (Day, Graham et al., 1987). Inflamed joints concentrate NSAD's because the pH of the synovial fluid is much lower than non-inflamed joints. For example, the synovial concentration of OPBZ was higher in human patients with severe inflammation than in those with no or little inflammation (Gaucher, Netter et al., 1983). Similar observations were made in an inflammatory carrageen rat paw model where the concentrations of C^{14}PBZ was approximately 800 fold greater that plasma (Graf, Glatt et al., 1975).

NSAID are highly protein bound, but effect of protein-binding may be more apparent than real as bound drug will dissociate as fast as free drug diffuses out (Simkin, 1988). In inflammatory joint diseases albumin-bound fraction diffuses better due to the increased capillary permeability to proteins (Netter, Bannwarth et al., 1989). Therefore the concentration of the NSAID will be higher in inflamed tissues.

NSAID have been classified in 2 categories on the basis of their half-lives. Drugs with a short half-life, shortly after administration, the concentration in synovial fluid is lower than in plasma but is reversed as the plasma concentration declines. In the horse, ketoprofen was no longer detectable in plasma after 5 h whereas synovial fluid concentrations were detected for 8 hours. In the same study carprofen with a half-life 10 times longer than ketoprofen, the concentrations in synovial fluid were significantly lower that plasma at all time points (Armstrong, Tricklebank et al., 1999). In rheumatoid patients on chronic therapy this may be a possible reasons for the drug's extended duration of action of drugs with apparent short elimination half-lives in plasma (Fowler, Shadforth et al., 1983). On the other hand, drugs with a longer half-life such as PBZ, the peak concentrations in synovial fluid were lower than plasma, remain lower and decrease in a parallel with the plasma concentration (Netter, Bannwarth et al., 1983). This difference in the pharmacokinetics based on elimination half-live was observed in horses with no joint disease. Following the IV administration of naproxen, synovial concentrations peaked at ~8 hours; were lower and followed a parallel decline in plasma and synovial fluid concentrations for up to 36 hours. There were no differences in the secondary disposition rate constant for plasma and elimination rate constants for the synovial fluid indicating a parallel decline in both concentration of naproxen (Soma, Uboh et al., 1995). Although this study has not been performed for PBZ in the horse similar relationships would be expected as the pharmacokinetics are similar (Soma, Gallis et al., 1983).

These differences based on the pharmacokinetic characteristics of the drug, delays in achieving synovial fluid concentrations and more importantly in assessing the effects of the administered drug to a diseased subject make it difficult to establish correlations between plasma concentrations and therapeutic response (Famaey, 1985). In human patients with osteoarthritis the synovial fluid concentrations of PBZ were lower than plasma, but correlated well. In human patients with rheumatoid arthritis synovial PBZ concentrations were higher based on the greater inflammatory nature of the disease and a higher synovial fluid protein concentration (Farr,

Hawkins et al., 1982). In clinico-pharmacological study in humans a relationship was present between dose, plasma concentration and clinical effects of PBZ (Brooks, Walker et al., 1975).

Many authors have suggested that the plasma concentrations of NSAID do not correlate well with assessments of therapeutic response. This may reflect weaknesses in experimental design, capability of determining the changes in pain levels and inflammation, and in clinical studies the variability in the diseases being studied. It may be that concentrations in plasma bear only a distant relationship to those in the inflamed tissues where NSAID presumably act (Famaey, 1985; Grennan, Aarons et al., 1985; Simkin, 1988). Compared to the CNS, NSAID readily penetrate the joint and the concentrations are not limited to the unbound fraction and will vary with the synovial environment. Studies in non-diseased joints are useful to describe the relative relationships and pharmacokinetics of the drug, but may have little relationship in the diseased joint. Despite the many studies and years of its use in the horse, plasma synovial relationships in the non-diseased and naturally occurring diseased joint have not been reported.

Naturally occurring osteoarthritis.

In a randomized controlled clinical trial, efficacy and safety of paste formulations of firocoxib (Equioxx®) and PBZ in horses with naturally occurring osteoarthritis were compared. Horses were treated with firocoxib (0.1 mg/kg, orally every 24 h) or PBZ (4.4 mg/kg, orally every 24 h) for 14 days. Clinical improvement was defined as a reduction of at least 1 lameness score grade or a combined reduction of at least 3 points in scores for pain during manipulation or palpation, joint swelling, joint circumference, and range of motion. Results obtained suggested some greater improvement in some categories tested than others following firocoxib, but overall clinical efficacy of firocoxib and PBZ in horses were comparable (Doucet, Bertone et al., 2008).

Horses with naturally occurring forelimb and hind limb lameness were exercised on a treadmill and the degree of lameness evaluated by the use of kinematic analysis while horses were trotting on the treadmill. Horses entered into the study were judged to have AAEP lameness scores of 1 to 3 based on a scale of upper severity score of 5 (Ross, *Lameness in the Horse* et al., 2003). In a cross-over study, PBZ paste was administered at 2.2 mg/kg (orally every 12 h for 5 days), alone or in combination with flunixin meglumine administered at 1.1 mg/kg, (IV every 12 h for 5 days). Lameness evaluations were performed before and 12 hours after administration of two NSAID treatment regimens. Administration of a combination of the two NSAID alleviated lameness more effectively than did oral administration of PBZ alone. Based on the authors' conclusion, when evaluating all 28 horses, there was a significant clinical improvement after the administration of both drugs in all horses except 5 with forelimb lameness. PBZ alone did not result in significant clinical improvement in all horses. Results of this study suggested that the use of combinations of NSAID (stacking) did have a better effect at 12 hours and would have a greater effect at 24 hours and the "stacking of drugs" should be a real concern. (Keegan, Messer et al., 2008).

The analgesic effects of PBZ in 9 horses with chronic forelimb lameness were studied. The horses were administered saline for control or PBZ at 4.4 and 8.8 mg/kg IV daily for 4 days. Peak vertical force (force plate) was measured and AAEP clinical lameness scores were assigned

before initiation of each treatment. All horses were evaluated 6, 12, and 24 hours after the final dose. The vertical force was significantly increased at all post-treatment evaluation times after PBZ compared to control horses. Clinical lameness and vertical force scores were significantly decreased at 6 and 12 hours at both doses and no differences were observed between the low or high dose. Scores were significantly decreased 24 hours after treatment only when PBZ was administered at the high dose (Hu, MacAllister et al., 2005).

Force plate analysis and the AAEP lameness scoring system were used to evaluate the analgesic efficacies of flunixin (1.1 mg/kg), PBZ (4.4 mg/kg), or physiologic saline solution administered IV in 12 horses with navicular syndrome. Medications were administered once daily for 4 days with a 14-day washout period between treatments. At 6, 12, and 24 hours after the fourth treatment, AAEP lameness evaluations and force plate data indicated significant improvement in lameness from baseline values in horses treated with flunixin or PBZ, compared with saline-treated control horses. The effect of flunixin or PBZ was maintained for at least 24 hours but no differences from control were noted at 30 hours. Flunixin meglumine and PBZ appear to have similar analgesic effects in horses with navicular syndrome (Erkert, MacAllister et al., 2005).

The analgesic effects of the NSAID, ketoprofen at 2.2 and 3.63 mg/kg and PBZ at 4.4 mg/kg were compared in 7 horses with bilateral forelimb chronic laminitis. Hoof pain was quantified objectively by means of an electronic hoof tester and lameness was subjectively graded on a modified Obel scale (Obel, 1948). Ketoprofen administered at 3.63 mg/kg (equimolar to 4.4 mg/kg of PBZ) reduced hoof pain and lameness score to a greater extent than the 2.2 mg/kg dose of ketoprofen or the 4.4 mg/kg of PBZ. These data suggest that ketoprofen at 1.65 times the recommended therapeutic dose was more potent than PBZ in alleviating chronic pain and lameness in horses. Phenylbutazone (4.4 mg/kg) and high dose of ketoprofen were still effective at 24 h (Owens, Kamerling et al., 1995).

Horses (12) with navicular syndrome were fitted with 3 degrees heel-elevation horseshoes and a force plate was used to measure baseline peak vertical ground reaction force (PVGRF) of the forelimbs. Vertical force was measured 24 hours and 14 days after shoeing and 24 hours following the administration of PBZ (4.4 mg/kg, IVq 12 h) for 5 days. There was further significant improvement in vertical force measured 24 hours following PBZ treatment. Heel-elevation shoeing alone and in combination with PBZ administration quantitatively decreased lameness in horses with navicular syndrome; injection of distal interphalangeal joint with triamcinolone acetonide did not significantly improve the vertical force measurements (Schoonover, Jann et al., 2005).

Induced lameness models.

The objective was to test the hypothesis that PBZ alleviates lameness in an adjustable heart bar-shoe model of equine foot pain following a single IV dose of 4.4 mg/kg. Heart rate and lameness score (1-5) were assessed every 20 min for 2 h and then hourly through 9 h. A lameness grade of 4 was produced for the study and no lameness was observed following the study when the set screw was removed. In the PBZ-treated horses the lameness score was lowest

between 4-5 h post-treatment when the score was reduced from 4 to 1.5 compared to control horses. Phenylbutazone was efficacious in alleviating lameness in this model. The PBZ plasma concentrations were approximately 15 and 7 μg/ml at 4 and 8 hours, respectively. The study period did not include observations beyond 9 hours, but the lameness score had not recovered to baseline values at that time (Foreman, Barange et al., 2008).

Lipopolysaccharide-induced synovitis was produced in horses and treated with PBZ (4.4 mg/kg, IV, q12h), or etodolac (23 mg/kg, IV, q12h). Both reduced synovial fluid white blood cell counts at 6 and 24 hours. In addition, both drugs significantly reduced PGE_2 levels at 6-h, but TXB_2 was only reduced by PBZ (Morton, Campbell et al., 2005). Using a standardized lameness model, flunixin was studied and PBZ was used in the same model as a positive control. At a dose of 4.4 mg/kg of PBZ and 1.1mg/kg of flunixin peak effect occurred at 8-12 and 12 hours, respectively. Flunixin analgesic activity persisted for 30 hours and PBZ for 24 hours (Houdeshell & Hennessey, 1977).

An induced arthritis model was developed to establish the relationship between the plasma concentration of PBZ and its pharmacological effects. Using experimental parameters, a dose-effect relationship was shown for PBZ with an absence of effect for the 1 mg/kg dose and a maximum effect at about 2 mg/kg; at higher PBZ doses, the maximum effect was not modified, but its duration was increased from 8 h with a 2 mg/kg dose to about 24 h with an 8 mg/kg dose (Toutain, Autefage et al., 1994). This study and others cited in this review came to the same conclusion that the maximum dose was 2.2 mg/kg and higher doses did not increase the effect except the duration. Similar results were noted in humans, a dose-finding study determined that most efficacious dose was 300 mg/day. Doses below this did not produce full benefit and no further improvement occurred with higher doses (Bird, Leatham et al., 1983).

The production of muscle inflammation by the injection of Freud's adjuvant did not affect the plasma kinetics and when administered 5 weeks apart there was no within horse variability indicating that the administration of PBZ did not affect the plasma kinetics of subsequent doses (Mills, Ng et al., 1996). This is verified by clinical observations that the plasma concentrations in a large population of horses are consistent post-race when a routine administration schedule was established in a horse and previous administrations do not affect subsequent doses.

Indirect assessment of duration of NSAID effects

It has been shown that the mechanism of the action of aspirin-like compounds was a direct inhibition of prostaglandin synthetase, thereby preventing prostaglandin biosynthesis (Vane, 1971; Moncada, Ferreira et al., 1974; Vane & Botting, 1987). These products of prostaglandin biosynthesis such as prostaglandins and prostacyclin produce hyperalgesia associated with inflammation and may cause pain and incapacity in some inflammatory conditions by sensitizing the chemical receptors of afferent pain endings to other inflammatory mediators such as bradykinin and histamine. NSAID are potent inhibitor of the conversion of arachidonic acid to arachidonic acid-derived mediators of inflammation. The site of action of NSAID is the cyclooxygenase pathway, therefore, blocking the synthesis and release of several chemical mediators of inflammation, collectively known as eicosanoids. Non-steroidal anti-

inflammatory drugs in the normal therapeutic doses do not block the lipoxygenase pathways which may be responsible for the reduction of leukocyte migration into the inflammatory site and the reduction of edema (Higgs, 1980).

Cyclooxygenase (COX-1) was the first enzyme recognized for catalyzing the synthesis of prostanoids from arachidonic acid, since this initial description a second isoform COX-2 has been described. Phenylbutazone is primarily a non-selective COX inhibitor; in vitro analysis in horse blood showed a greater COX-1 selectivity determined by the depression of TXB_2, compared to COX-2 selectivity determined by the depression of PGE_2 (Beretta, Garavaglia et al., 2005). This observation confirms that in the horse, PBZ is a more selective inhibitor of COX-1 than COX-2. This is relevant in that species difference have been noted in the concentrations of the stable metabolite TXB_2 released by COX-1 activation and the concentration of PGE_2 release by lipopolysaccharide activation of COX-2 and the selective inhibition by various NSAID (Brideau, Van Staden et al., 2001).

There have been considerable advances in the development of pharmacokinetic/pharmacodynamic (PK/PD) models in veterinary and human medicine and investigators have studied the effects of the drug and concurrent changes in plasma or tissue concentrations of inflammatory mediators. Modern PK/PD studies link the effect(s) of the drug to its corresponding concentration in plasma (Lees, 2004; Lees, Cunningham et al., 2004; Lees, Giraudel et al., 2004; Toutain & Lees, 2004). General PD/PK models have been developed for describing drug actions on various active metabolites and hormones (Krzyzanski & Jusko, 2001; Puchalski, Krzyzanski et al., 2001).

A number of studies have used the reduction in the metabolic products of inflammation as indirect models of the actions of PBZ and other NSAID at the molecular level to determine the degree and duration of action. Three types of models have been used:

1. Suppression of the release of inflammatory mediators in blood samples. A number of PK/PD models have been developed using this technique (Lees, Ewins et al., 1987; Soma, Uboh et al., 1992; Lees, Giraudel et al., 2004; Lees, Landoni et al., 2004).
2. Suppression of the release of inflammatory mediators in tissue cage and sponge models in which a sterile carrageen solution was injected into the cage or sterile carrageen-soaked polyester sponge strips were inserted subcutaneously. Both were based on the creation of a mild, reproducible and reversible inflammatory reaction that causes minimal distress to the experimental animals. The acute inflammatory exudates have been shown to contain proteins, white blood cells, and eicosanoids all as a result of the inflammatory reaction (Higgins & Lees, 1984; Lees & Higgins, 1984; Higgins, Lees et al., 1987; Lees, Higgins et al., 1987).
3. More recently, models in humans have used flow through methods to harvest inflammatory exudates. In-vivo human bioassay can be used to study human volunteers and patients. Samples are collected from pertinent tissue sites such as the skin via aseptically inserted micro dialysis catheters. These experiments measured inflammatory

substances in interstitial fluid collected from non-inflamed and experimentally inflamed skin (Angst, Clark et al., 2008; Angst, Tingle et al., 2008).

Indirect Plasma Models

A study involving the inhibitory actions of NSAID on TXB_2 following a single dose of flunixin (1.1 mg/kg) or PBZ (4.4 mg/kg) was used to determine the duration of action of these drugs. Flunixin and PBZ produced similar degrees of reversible inhibition of TXB_2 at 4 (98% and 88%), 8 (77% and76 %), and 24 (63 and 50 %) hours, respectively. At 48 hours, inhibition of TXB_2 was no longer apparent (Lees, Ewins et al., 1987).

In a similar study the concurrent administration of flunixin meglumine (1.1 mg/kg, IV) and PBZ (2.2 mg/kg, IV) on the pharmacokinetics of each drug indicated that the pharmacokinetic variables calculated for each drug when administered alone and in combination were similar. Serum TXB_2 production was significantly suppressed for 8, 12, and 24 hours after administration of flunixin and PBZ in combination. When these drugs were administered alone, the TXB_2 concentrations were not significantly different from control values at 24 h. Note in this study that the dose of PBZ was 2.2 mg/kg. (Semrad, Sams et al., 1993).

Indirect Tissue Models.

Distribution of PBZ and its active metabolite, OPBZ, into tissue fluids was studied by measuring concentrations in plasma, tissue-cage fluid, peritoneal fluid and acute inflammatory exudates harvested from a polyester sponge model of inflammation in ponies. Phenylbutazone and OPBZ readily penetrated into inflammatory sites. After six hours, the concentration of PBZ was higher in exudates than in plasma and remained so at 24 hours. Mean concentrations of OPBZ in all fluids were lower than those of PBZ at all times, but OPBZ readily entered body fluids, especially into inflammatory exudates; suggesting that OPBZ may contribute to the anti-inflammatory effect. The estimated elimination half-life of PBZ from exudates was 24 h compared to 5 h from plasma. These authors suggested that the persistence of PBZ and OPBZ in tissues exudates extended the duration of PBZ effectiveness (Lees, Taylor et al., 1986). Other studies have shown that flunixin was also cleared more slowly from equine tissue inflammatory exudates than from plasma (Higgins, Lees et al., 1987).

Acute inflammation was induced in 7 ponies by subcutaneous implantation of sterile carrageen-soaked polyester sponge strips. Treatment comprised a single therapeutic dose of 4.4 mg/kg of PBZ administered intravenously at the time of sponge implantation. Exudates were harvested at 6, 12 and 24 hours and examined for leukocyte and erythrocyte numbers. Leukocyte numbers were significantly increased from 6-hour values at 12 and 24 hours in both control and PBZ-treated animals but differences between control and treated ponies were not significant. The administration of PBZ produced significant reductions in exudate concentrations of PGE_2 and 6-keto-$PGF_1\alpha$, the stable products of prostacyclin at 6, 12, and 24 hours. Concentrations of PBZ and OPBZ in exudates exceeded the plasma concentrations in plasma at 12 and 24 hours. Concentrations of TXB_2, the stable products of TXB_2, were reduced in treated animals but these changes were not significant. Study results suggested an effect at 24

hours based on the reduction of the two measured eicosanoids PGE_2 and 6-keto-$PGF_1\alpha$ (Higgins, Lees et al., 1984).

In a 12-day treatment schedule, 5 ponies were administered an oral paste formulation of PBZ and 5 matched ponies were administered equivalent doses of a placebo paste. On day 12, a mild, non-immune inflammatory reaction was induced subcutaneously. Exudates were collected at 4, 8, 12, and 24 hours. There were no significant differences in exudate protein concentration and leukocyte numbers between the treatment groups, but exudate concentrations of 6-ketoF1α were reduced at 4, 8, and 12 hours and those of TXB_2 at 8, 12, and 24 h in the PBZ treatment group. The increases in surface skin temperature were significantly less in PBZ-treated than in placebo-treated ponies between 4 and 24 hours (Lees & Higgins, 1986).

The hypothesis of prostaglandin synthetase inhibition is the most widely accepted mode of action for NSAID. In one hand, leukocyte and erythrocyte accumulation in exudates is a part of the inflammatory process was not significantly affected by the NSAID in any of the tissue cage and exudates studies (Lees & Higgins, 1984; Lees & Higgins, 1986). In the other hand, in-vitro studies have shown that flunixin, PBZ, OPBZ, and indomethacin suppress leukocyte migration of which flunixin was the most potent of the 4 drugs studied. The obvious difference between in-vivo and in-vitro studies is the more complex environment of the inflamed joint compared to the controlled environment of an in-vitro study (Dawson, Lees et al., 1987).

SUMMARY:

This review presented an historical prospective and examined the information presented in 4 different models used to determine the pharmacological effects of NSAID, especially PBZ. They included naturally occurring lameness, reversible induced lameness, and indirect plasma and tissue models studying the suppression of the release of arachidonic-derived mediators of inflammation. The majority of studies suggest a persistent effect of PBZ at 24 hours at 4.4 mg/kg. This reflects and substantiates the opinion of many clinical veterinarians, many of whom will not examine a horse for a pre-purchase lameness examination unless the horse is shown to be free of NSAID and glucorticoids. This remains the opinion of many Commission Veterinarians in that they wish to examine a horse pre-race without the possibility of NSAID or corticosteroid interfering with the examination and masking a possible musclo-skeletal condition. Based on scientific reports and the impression of clinical veterinarians, residual effects of PBZ remain at 24 hours. The impact of this sustained effect on the health and welfare of the horse remains problematic.

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ITEM III.

POTENTIAL CHANGES TO THE BLEEDERS AND FUROSEMIDE PROGRAM

1. Texas Rules of Racing
Section 319.111 Bleeders and Furosemide Program,
Pages 33-34

2. RCI Model Rule
ARCI-011-020 Medications and Prohibited Substances
Item F. Furosemide,
Pages 35 - 36

3. Request by TQHA to amend provisions relating to horses voluntarily admitted to Program,
Pages 37-40

TEXAS RACING COMMISSION
RULES OF RACING
Sec. 319.111. Bleeders and Furosemide Program.

(a) Diagnosis of EIPH.

(1) A bleeder is a horse that experiences Exercise Induced Pulmonary Hemorrhage (EIPH). Except as otherwise provided by this subsection, the medical diagnosis of EIPH may be made only by a commission veterinarian or a veterinarian currently licensed by the Commission. If the first EIPH event experienced by a horse occurs in another pari-mutuel racing jurisdiction, certification of the horse as a bleeder by that foreign jurisdiction will also constitute a first report of a diagnosed EIPH event for purposes of this section. A veterinarian who diagnoses an EIPH event in a horse participating in pari-mutuel racing in this state shall report the event to the commission veterinarian in a format prescribed by the executive secretary. On receipt of the first report of a diagnosed EIPH event for a horse, the commission veterinarian shall certify the horse as a bleeder.

(2) A trainer may request that a commission veterinarian reconsider the commission veterinarian's diagnosis of an EIPH event by presenting the horse for re-examination within four hours of the initial diagnosis, or within one hour after a performance's last race, whichever occurs sooner. To receive reconsideration, the trainer must present the horse to the commission veterinarian for endoscopic examination as performed by a commission-licensed veterinarian.

(b) Admission to Furosemide Program.

(1) A trainer may admit a horse to the furosemide program by stating at time of entry that the horse will compete with furosemide.

(2) A horse that competed with furosemide in its most recent start out-of-state must compete on furosemide in Texas unless withdrawn from the furosemide program at time of entry.

(3) An EIPH event experienced by a horse that is admitted to the furosemide program is deemed to be a second EIPH event for purposes of Subsection (g) of this section.

(c) Administration of Furosemide. Furosemide shall be administered to a horse in the furosemide program not later than four hours before the published post time for the race the horse is entered to run. The furosemide must be administered intravenously by a veterinarian licensed by the Commission. The executive secretary shall periodically publish the permissible blood levels of furosemide in post-race specimens and shall post the levels at each licensed racetrack.

(d) Requirement to Use Furosemide. A horse in the furosemide program in Texas must compete with furosemide until withdrawn from the program.

(e) Withdrawal from Furosemide Program.

(1) To withdraw a horse from the furosemide program, the trainer must state his/her intention to race the horse without furosemide at the time of entry.

(2) A horse in the furosemide program that competes out-of-state without furosemide is considered to have been removed from the Texas furosemide program effective the date of its first race without furosemide.

(3) Withdrawal from the furosemide program does not prohibit a horse from subsequent readmission to the program in accordance with this section.

(f) Readmission to the Furosemide Program. A horse may be readmitted to the furosemide program if:

(1) at least 60 days have elapsed since the horse was withdrawn from the program;

(2) the horse is required to compete with furosemide pursuant to subsection (b)(2) of this section; or

(3) the commission veterinarian diagnoses the horse with another EIPH event.

(g) Bleeders List.

(1) The commission veterinarian shall maintain a list of horses that have been certified as bleeders and a list of horses that have been admitted to the furosemide program.

(2) On receipt of a report of a diagnosed EIPH event, the commission

veterinarian shall place the horse on the veterinarian's list and the horse shall be ineligible to race for the following time periods:

First incident - 12 days;

Second incident within 365 days of previous incident - 30 days;

Third incident within 365 days of previous incident - 180 days;

Fourth incident within 365 days of previous incident - lifetime ban from racing in this state.

(3) A horse with fewer than four EIPH events that has not had a diagnosed EIPH event for a period of 365 consecutive days is considered a non-bleeder for purposes of this subsection. The report of a diagnosed EIPH event from any pari-mutuel jurisdiction which officially records EIPH events will be recognized as an EIPH event by the Commission.

(4) Notwithstanding the foregoing, if after reviewing a report of a diagnosed EIPH event the commission veterinarian determines additional days on the veterinarian's list are essential to the health and safety of the horse, the commission veterinarian may extend the number of days the horse is on the veterinarian's list. The commission veterinarian shall record the medical reasons for the additional days.

(h) Report by Veterinarian. A veterinarian who administers furosemide to a horse that has been admitted to the furosemide program shall report the administration on a form prescribed by the Commission. A report made under this subsection must be filed with the test barn supervisor not later than one hour before post time for the first race of that day. (Added eff. 11/3/89; (a),(b),(h) amended eff. 8/3/92; (c)-(g) added eff. 8/3/92; (b), (c),(h) amended eff. 4/28/94; (c),(d),(f),(g) amended eff. 11/1/94; (b) amended eff. 3/15/95; (g) amended eff. 1/3/96; amended eff. 5/1/96; (f) amended eff. 10/1/96; (b), (c),(e),(f) amended eff. 11/1/98; (g) added eff. 11/1/98; (b) amended eff. 2/15/99; (a) amended eff. 7/17/01; amended eff. 11/1/01; (b),(f) amended eff. 5/18/04; (a),(e),(f),(g) amended eff. 7/16/07)before the actual start time of the race. (Added eff. 8/14/89; (a),(b) amended eff. 10/11/90; amended eff. 11/1/98)

RCI MODEL RULE
ARCI-011-020 Medications and Prohibited Substances

F. Furosemide
(1) Furosemide may be administered intravenously to a horse, which is entered to compete in a race. Except under the instructions of the official veterinarian or the racing veterinarian for the purpose of removing a horse from the Veterinarian's List or to facilitate the collection of a post-race urine sample, furosemide shall be permitted only after the official veterinarian has placed the horse on the Furosemide List. In order for a horse to be placed on the Furosemide List the following process must be followed.

(a) After the horse's licensed trainer and licensed veterinarian determine that it would be in the horse"s best interests to race with furosemide they shall notify the official veterinarian or his/her designee, using the prescribed form, that they wish the horse to be put on the Furosemide List.

(b) The form must be received by the official veterinarian or his/her designee by the proper time deadlines so as to ensure public notification.

(c) A horse placed on the official Furosemide List must remain on that list unless the licensed trainer and licensed veterinarian submit a written request to remove the horse from the list. The request must be made to the official veterinarian or his/her designee, on the proper form, no later than the time of entry.

(d) After a horse has been removed from the Furosemide List, the horse may not be placed back on the list for a period of 60 calendar days unless it is determined to be detrimental to the welfare of the horse, in consultation with the official veterinarian. If a horse is removed from the official Furosemide List a second time in a 365-day period, the horse may not be placed back on the list for a period of 90 calendar days.

(e) Furosemide shall only be administered on association grounds.

(f) Upon the request of the regulatory agency designee, the veterinarian administering the authorized bleeder medication shall surrender the syringe used to administer such medication which may then be submitted for testing

(2) The use of furosemide shall be permitted under the following circumstances on association grounds where a detention barn is utilized:

(a) Furosemide shall be administered at the direction of the official veterinarian no less than four hours prior to post time for the race for which the horse is entered.

(b) A horse qualified for furosemide administration must be brought to the detention barn within time to comply with the four-hour administration requirement specified above.

(c) The dose administered shall not exceed 500 mg. nor be less than 150 mg.

(d) Furosemide shall be administered by a single, intravenous injection.

(e) After treatment, the horse shall be required by the Commission to remain in the detention barn in the care, custody and control of its trainer or the trainer's designated representative under association and/or Commission security supervision until called to the saddling paddock.

(3) The use of furosemide shall be permitted under the following circumstances on association grounds where a detention barn is not utilized:

(a) Furosemide shall be administered no less than four hours prior to post time for the race for which the horse is entered.

(b) The furosemide dosage administered shall not exceed 500 mg. nor be less than 150 mg.

(c) Furosemide shall be administered by a single, intravenous injection.

(d) The trainer of the treated horse shall cause to be delivered to the official veterinarian no later than one hour prior to post time for the race for which the horse is entered the following information under oath on a form provided by the Commission:

(A) The name of the horse, racetrack name, the date and time the

furosemide was administered to the entered horse;

(B) The dosage amount of furosemide administered to the entered horse; and

(C) The printed name and signature of the attending licensed veterinarian who administered the furosemide.

(4) Test results must show a detectable concentration of the drug in the post-race serum, plasma or urine sample.

(a) The specific gravity of post-race urine samples may be measured to ensure that samples are sufficiently concentrated for proper chemical analysis. The specific gravity shall not be below 1.010. If the specific gravity of the urine is found to be below 1.010 or if a urine sample is unavailable for testing, quantitation of furosemide in serum or plasma shall be performed;

(b) Quantitation of furosemide in serum or plasma shall be performed when the specific gravity of the corresponding urine sample is not measured or if measured below 1.010. Concentrations may not exceed 100 nanograms of furosemide per milliliter of serum or plasma

G. Bleeder List

(1) The official veterinarian shall maintain a Bleeder List of all horses, which have demonstrated external evidence of exercise induced pulmonary hemorrhage from one or both nostrils during or after a race or workout as observed by the official veterinarian.

(2) Every confirmed bleeder, regardless of age, shall be placed on the Bleeder List and be ineligible to race for the following time periods:

(a) First incident – 14 days;

(b) Second incident within 365 day period – 30 days;

(c) Third incident within 365 day period –180 days;

(d) Fourth incident within 365-day period – barred for racing lifetime.

(3) For the purposes of counting the number of days a horse is ineligible to run, the day the horse bled externally is the first day of the recovery period.

(4) The voluntary administration of furosemide without an external bleeding incident shall not subject the horse to the initial period of ineligibility as defined by this policy.

(5) A horse may be removed from the Bleeder List only upon the direction of the official veterinarian, who shall certify in writing to the stewards the recommendation for removal.

(6) A horse which has been placed on a Bleeder List in another jurisdiction pursuant to these rules shall be placed on a Bleeder List in this jurisdiction.

TEXAS RACING COMMISSION

COMMITTEE ON RULES

Date of Request: 10/26/2010

Request for Proposed Change to an Existing Rule or Addition of a New Rule to the Rules of Racing

Please submit this information to the attention of the Executive Director *at least 14 days* in advance of the next scheduled Committee on Rules meeting. An electronic form is available to assist in your submission or feel free to add additional pages as necessary in order to provide as much detail as possible. Filing this request does not guarantee that your proposal will be considered by the Committee on Rules.

Texas Racing Commission
8505 Cross Park Drive, Suite 110
Austin, TX 78754-4552
Phone: 512/833-6699 Fax: 512-833-6907
email: info@txrc.state.tx.us

Contact Information:

Name:	Rob Werstler	Phone(s):	512-458-5202
E-mail address:	rwerstler@tqha.com	Fax number:	512-458-1713
Mailing address:	1101 W. Anderson Lane, Austin, 78757		

☐ Personal Submission *OR*

☐ Submission on behalf of TQHA
(Name of Organization)

☒ If known, Proposed Change to Chapter: 319.111, Rule (b)(3)

☐ If known, Proposed Addition to Chapter: _____

☐ If known, Other Rules Affected by Proposal: _____

A. Brief Description of the Issue

Per Section 319.111 Bleeders and Furosemide Program (b)(3) "An Exercise Induced Pulmonary Hemorrhage (EIPH) event experienced by a horse that is admitted to the furosemide program by a trainer is deemed to have suffered a second EIPH event." This, even if the horse was admitted to the program voluntarily by the trainer and with no EIPH incident.

B. Discussion of the Issue and Problem

Provide background on the Issue to build context. Address the following:

- *What specific problems or concerns are involved in this issue?*
- *Who does the issue affect?*
- *What existing model rules relate to this issue?*
- *Provide relevant quantitative or statistical information if possible.*

Under the current rule, a horse competing and qualifying in trials that has been admitted voluntarily to the Bleeder Program and then suffers an EIPH event will not be eligible to run in the finals, as the horse is automatically put on the bleeders list and ineligible to race for 30 days. Most trials are only 14 days before the finals. This affects Quarter Horses who compete more regularly in trial races.

RCI Model Rule G. Bleeder List (4) states "The voluntary administration of furosemide without an external bleeding incident shall not subject the horse to the initial period of ineligibility as defined by this policy."

Texas currently has the most restrictive "bleeder" rule in the region- Oklahoma's rule is basically the same as the RCI rule where a trainer can admit a horse to the "Furosemide Program" and will not count as an EIPH incident. The first time the horse bleeds, if ever, will be deemed the first EIPH incident. In New Mexico, a horse can experience an EIPH incident every time it runs and there is no penalty.
I will supply the committee with furosemide rules from Louisiana, New Mexico and Oklahoma at the October 26 meeting

A south African study in 2008 determined that EIPH incidence and severity was improved by pre-race administration of lasix. It has also been determined that furosemide is as affective as a preventative as it is as a treatment.

C. Possible Solutions and Impact

Provide possible recommendations to solve the problem. Include details on each proposed solution such as:

- *What solution does this proposal provide?*
- *How will the solution fix the problem?*
- *How will the change affect any entities or stakeholders?*
- *How will you or your organization be affected by the proposed change?*
- *What are the benefits of the proposed change?*
- *What are the possible drawbacks of the proposed change?*
- *Identify possible fiscal impact of the recommended change.*

Modify Section 319.111 Bleeders and Furosemide Program (b) Bleeders by incorporating the intent of the RCI language: The first Exercise Induced Pulmonary Hemorrhage (EIPH) event experienced by a horse that a trainer has admitted voluntarily to the furosemide program will be considered the horse's first EIPH event for purposes of determining the number of days the horse is ineligible to race under Section 319.111 (g).

There have been incidents where an owner was not allowed to enter a horse back in to a final of a grade I, million dollar futurity because of the current rule language. If this horse had run well in the final it would have increased the value of the animal significantly. Also, there have been owners that have left Texas taken their horses to compete in races in other jurisdictions where the furosemide program is not as restrictive.

D. Support or Opposition

Please identify any affected stakeholder groups that expressed support or opposition. (These stakeholders may include the racetracks, breed registries, owners, kennel owners, trainers, jockeys, veterinarians, or others.)

- *For those stakeholder groups that have expressed an opinion, please list the points on which they agree or disagree, and the arguments they have expressed.*
- *Are there any affected stakeholder groups that have not been consulted on this proposal?*
- *Please submit any formal letters of support or opposition by stakeholder groups.*

I do not know of any groups opposed to this rule change.

E. Proposal

Provide rule language you are proposing. If you are proposing that current rule language be eliminated, please strikeout the language to be deleted. Please show new language with underlined text.

Sec. 319.111 Bleeders and Furosemide Program (b)(1) A trainer may voluntarily admit a horse to the furosemide program by stating at time of entry that the horse will compete with furosemide.

Sec.319.111 Bleeders and Furosemide Program (b)(3) "An EIPH event experienced by a horse that is voluntarily admitted to the furosemide program is deemed to be the first EIPH event for purposes of Subsection(g) of this section.

Sec.319.111 Bleeders and Furosemide Program (g)(2) Bleeders List: On receipt of a diagnosed EIPH event, the commission veterinarian shall place the horse on the veterinarian's list and the horse shall be eligible to enter but ineligible to race for the following time periods:

Furosemide (Salix, Lasix)

- SAFE Study:
  - Double-blinded study using horses that have never received furosemide before in actual race conditions for purse money in South Africa
  - Horses receiving saline instead of furosemide had increased severity of EIPH
  - 67.5% of horses that bled when receiving saline had improved EIPH severity scores by at least one when receiving furosemide instead
  - Conclusion…EIPH incidence and severity was improved by pre-race administration of furosemide

TQHA REQUESTED CHANGE SHOWING STRIKEOUT/NEW LANGUAGE

Sec. 319.111. Bleeders and Furosemide Program.
(a) Diagnosis of EIPH. No change
(b) Admission to Furosemide Program.
(1) No change..
(2) No change.
(3) An EIPH event experienced by a horse that is voluntarily admitted to the furosemide program is deemed to be ~~a second~~ the first EIPH event for purposes of Subsection (g) of this section.

Proposed change would read:
An EIPH event experienced by a horse that is voluntarily admitted to the furosemide program is deemed to be the first EIPH event for purposes of Subsection (g) of this section.