RMTC
Racing Medication & Testing Consortium

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Mr. Ed Martin
President
Association of Racing Commissioners International
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VIA ELECTRONIC MAIL

Dear Ed:

The RMTC SAC received your request on behalf of ARCI to review and comment on the attached proposal from the USTA. The proposal requests a change in the betamethasone and clenbuterol thresholds to allow for administration of these medications within 7 days of racing. Specifically, the proposal would:

- Increase the threshold in Standardbred Horses from 10 pg/ml to 100 pg/ml in plasma or serum for betamethasone and
- Change the threshold in Standardbred Horses from 140 pg/ml of urine to 25 pg/ml of plasma or serum for clenbuterol.

The RMTC SAC discussed this proposal at length and reviewed the existing science on these medications at its February 5, 2019 meeting. One unanimous message from the group was that the health and the welfare of the horse is paramount. Accordingly, the SAC members rejected the proposal for the following reasons:

Betamethasone:

- The dose in the proposal exceeds the manufacturer's recommended dose. The dose in the proposal exceeds the manufacturers recommended dose by almost two-fold.[i] The proposal lacks justification for administration of betamethasone in this manner. In fact, a recent study showed that "maximum anti-inflammatory activities for the glucocorticoids were observed at *in vitro* concentrations below manufacturer recommended levels."[1]

- Betamethasone persists in the joint fluid of the treated joint beyond 14 days. The fact that measurable concentrations of the drug are in contact with target tissues in the joint supports an extended duration of effect.[2] As such, the current RMTC threshold permits therapeutic use of betamethasone with an appropriate withdrawal period to safeguard the health and welfare of the horse.

[i] Federal code allows a veterinarian to legally elect to administer a product at a dose that differs from the manufacturer's recommendation.

The AAEP White Paper entitled Clinical Guidelines for Veterinarians Practicing in a Pari-Mutual Environment states that "[s]cientific research has demonstrated that most of the commonly used IA corticosteroids produce prolonged periods of therapeutic effect measured in weeks."[3]

- The USTA's Position Paper states "[t]he regulatory concern is that betamethasone could mask injury and therefore place the horse at risk of further injury. Specifically, if betamethasone were administered too close to race time, horsemen and veterinarians would be unable to assess response to treatment before putting the horse at risk by racing."

  The RMTC SAC did not accept that the purported 6 ½ day withdrawal guidance based upon the proposed threshold allows for appropriate evaluation of a horse post-race and prior to treatment. Simply, the suggested threshold of 100 pg/ml in plasma/blood is permissive of an intra-articular injection(s) within less than 48 hours of racing.[4] This precludes assessing a response to treatment before putting a horse at risk by racing.

- The argument that 'Standardbred Horses are required to race every week' does not contemplate the health and welfare of the horse. Dr. Wayne McIlwraith, acknowledged to be one of the leading experts on orthopedic disease in the horse, stated that thresholds "designed to minimize IA injection within 7 days of racing are appropriate and can be defended scientifically."[5]

- The USTA proposal characterized intra-articular treatment with corticosteroids as prophylactic. There is no clinical indication for the administration of intra-articular corticosteroids in a healthy joint.

  Corticosteroids are symptom modifying but not disease modifying. The administration of intra-articular corticosteroids in the absence of an appropriate diagnosis is unwarranted.

- The RMTC recognized the therapeutic value of judiciously used intra-articular corticosteroids but a horse's health should dictate its return to racing.

Clenbuterol:

- The proposal contemplates the use of clenbuterol for 3-3½ days post-racing with a 4-day withdrawal period prior to the next race. The medical rationale and data supporting the safety and efficacy of this approach was not provided.

  The manufacturer's recommendation is a 30-day treatment regimen for the treatment of Inflammatory Airway Disease and Recurrent Airway Obstruction.[6] Neither of these conditions are referenced in the proposal. Rather, it discusses the clearance of debris from the airway that could addressed using an expectorant such as guaifenesin which has a 48-hour withdrawal time.

- The USTA's proposal states "[t]he regulatory concern is that clenbuterol, if administered too close to the time of an upcoming race, might enhance performance by reducing normal respiratory secretions occurring during racing, or by improving respiratory

function in some other way." This fails to acknowledge the documented anabolic-like effects of clenbuterol. These effects are expressed following as few as three days of treatment.[7] There is no research showing the absence of anabolic effects with a 4-day withdrawal period following 3 days of treatment.

- Further, the proposal's recommended threshold allows race-day intra-tracheal administration of clenbuterol to occur while evading laboratory detection.[8] While not studied, there is also the potential for inhaled clenbuterol to be permitted on race day under this threshold.

  Given that samples are collected at approximately 1-hour post-race, the 25 pg/ml proposed threshold is permissive of a treatment that has the potential to exert a bronchodilatory effect at the time of the race.[9]

  In a study involving 30 days of clenbuterol administration at 0.8 mgc/kg the average concentration of clenbuterol in plasma was well below 25 pg/ml in plasma at 48 hours.[10] Based upon the proposed threshold, a horse could be dosed beginning the day of racing until 48 hours prior to racing a week later – a total of 5 days. This would mean Standardbred race horses could be dosed 260 days per year – even if they raced weekly.

- The USTA proposal fails to acknowledge the welfare concerns associated with long-term clenbuterol administration. Statistically significant changes in cardiac function have been measured with as few as eight weeks of clenbuterol administration. These included changes to stroke volume, left ventricle internal dimension, and increased aortic root dimension.[11]

- Clenbuterol treatment should be reported to the regulatory authority and subject to a valid veterinary client patient relationship. The RMTC threshold protects against race-day administrations as well as dosage regimens designed to achieve anabolic effect.[12] The USTA proposal is permissive of both.

- The desire to race a horse approximately weekly should not supersede the health and welfare of the horse.

In addition to these critical deficiencies, the USTA's proposal incorrectly characterizes the statistical method utilized by the RMTC to develop thresholds and/or withdrawal guidance as having a 1:20 risk of a positive test. In the states having adopted the RMTC's recommended threshold of 140 pg/ml only 2 positives were reported in Standardbred racing in 2018. Based upon the proposal's assessment that compliance with withdrawal guidance results in a 1:20 risk of a positive test, one can conclude that only 40 horses that were treated with clenbuterol were tested. If this is the case, then clearly clenbuterol use in Standardbred racing is a non-issue.

In summary, if adopted, the proposed thresholds for betamethasone and clenbuterol would allow unscrupulous trainers and veterinarians to administer these agents within the withdrawal times recommended by the USTA. Accordingly, the proposed thresholds represent a threat to the integrity of the sport. The medical consequences of these dosing regimens are unknown and thus they represent a threat to the health and safety of the horse.

This statement was also reviewed by the RMTC Board and passed with one vote against (The Hambletonian Society) and two abstentions (ARCI and HBPA).

Please let me know if you have any additional questions. Thank you.

Dionne M. Benson, JD, DVM
Executive Director and COO

References

[1] Zhu, W. *Glucocorticoid-Induced Chondrocyte Cytotoxicity at Doses Recommended for Intra-articular Therapy in Horses*, (2015) available on-line at: https://uknowledge.uky.edu/cgi/viewcontent.cgi?article=1023&context=gluck_etds.

[2] Knych, H. *et al.*, *Pharmacokinetics of Betamethasone in Plasma, Urine, and Synovial Fluid Following Intra-Articular Administration to Exercised Thoroughbred Horses*, (2017) Drug Test. Analysis 9:1385-91.

[3] American Association of Equine Practitioners Racing Committee, *Clinical Guidelines for Veterinarians Practicing in a Pari-Mutual Environment*, August 2010 *citing* McIlwraith, C.W., *Use of Intra-Articular Corticosteroids in the Horse-What is Known on a Scientific Basis*, EVJ (2010) Sept; 42(6): 563-71.

[4] Knych, H. *et al.*, *Pharmacokinetics of Betamethasone in Plasma, Urine, and Synovial Fluid Following Intra-Articular Administration to Exercised Thoroughbred Horses*, (2017) Drug Test. Analysis 9:1385-91.

[5] McIlwraith, C.W., *et al.*, Joint Disease in the Horse, Second Edition, 2015 Elsevier Health Sciences, p. 210.

[6] Ventipulmin drug label information, available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=691e6c6a-0ac6-4cc2-bd87-954bf6716735.

[7] Nolen-Watson, R., *et al.*, *Effect of Long-term Oral Administration of a Low Dosage of Clenbuterol on Body Fat Percentage in Working and Nonworking Adult Horses*, Am J Vet Res (2015) May; 76(5): 460-66.

[8] Lehner, A.F., *et al.*, *Clenbuterol in the Horse: Confirmation and Quantitation of Serum Clenbuterol by LC-MS-MS after Oral and Intratracheal Administration*, Journal of Analytical Toxicology (2001) May/June; 25:280-87.

[9] Robinson, N.E., *Clenbuterol and The Horse*, Proceedings of the Annual Convention of the AAEP (2000) Volume 46: 229-233.

[10] Knych, H.K., *et al.*, *Detection, Pharmacokinetics and Cardiac Effects Following Administration of Clenbuterol to Exercised Horses*, Equine Vet J. (2014) May; 46(3): 380-85.

[11] Sleeper, M.M., *et al.*, *Chronic Clenbuterol Administration Negatively Alters Cardiac Function*, Medicine and Science in Sports and Exercise (2002) Apr.; 34(4): 643-50.

[12] Knych, H.K., *et al.*, *Detection, Pharmacokinetics and Cardiac Effects Following Administration of Clenbuterol to Exercised Horses*, Equine Vet J. (2014) May; 46(3): 380-85.