National Horsemen's Benevolent & Protective Association, Inc.

Proposed National Policy on Drug Testing and Therapeutic Medication Regulation

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LAY SUMMARY

The National Horsemen's Benevolent and Protective Association (NHBPA) fully supports a zero tolerance policy for performance-altering substances and prohibited practices including but not limited to administration of milkshakes, erythropoietins, growth hormones, and unregulated shock-wave therapy.

Zero tolerance policy testing means testing at the highest available level of sensitivity and is therefore constantly changing. An ever-changing policy is, by definition, inappropriate for regulation of therapeutic medications and endogenous, dietary, and environmental substances. Standardized testing across the nation is the only viable approach to such testing, not the ever-changing zero tolerance policy approach.

Standardized testing means regulatory thresholds. The NHBPA now therefore proposes regulatory thresholds for the 50-plus therapeutic medications recognized by the America Association of Equine Practitioners (AAEP) and the Racing Medication and Testing Consortium (RMTC). Regulatory thresholds are also required for the 10-plus endogenous, dietary, and environmental substances readily identifiable in racing samples that are also performance-altering substances.

To enable horsemen to comply with these thresholds, "withdrawal time guidelines" scientifically linked to these thresholds are required. Few such scientifically determined and published withdrawal time guidelines linked to regulatory thresholds are available; development of such withdrawal time guidelines is a priority goal of the RMTC, and these efforts are fully supported and endorsed by the NHBPA.

This policy addresses the need for publication in the scientific literature of the research basis for regulatory thresholds and linked withdrawal time guidelines. The need for national standards/accreditation for drug testing laboratories is addressed with an emphasis on increased use of blood testing to advance the science of medication regulation in racing horses.

Standardization of testing requires access to certified reference standards. In support of standardized testing, the National and Regional Horsemen's Benevolent and Protective Associations have long supported research on regulatory thresholds, including the synthesis and worldwide distribution of the certified reference standards on which standardized testing is based.

Background and Acknowledgments

This National Policy was inspired by Mr. Ted Bassett, President of the Keeneland Association, who in 2001 suggested to Mr. Don Sturgill, Esq., General Counsel to the National HBPA, that the HBPA develop a national medication policy. This suggestion of Mr. Bassett's resonated with that made by Kent Stirling of the Florida HBPA at the summer HBPA meeting in Boston in 2001. Don immediately alerted President John Roark and Executive Director Remi Bellocq of the National HBPA, and within days Kent and Dr. Thomas Tobin, with the assistance of Remi Bellocq and the National HBPA Medication Committee, began drafting this policy. This document, therefore, is a tribute to the leadership and foresight of Mr. Ted Bassett, Kent Stirling, Don Sturgill, John Roark, and Remi Bellocq, and all the members of the National HBPA Medication Committee.

The Medication Committee was well positioned to draft this document. Starting in 1994, under President Mel Bowman, the HBPA began supporting research on thresholds for therapeutic medication regulation. In August of 1994, the HBPA supported an international workshop on "Testing for Therapeutic Medications, Environmental and Dietary Substances in Racing Horses" at the Maxwell H. Gluck Equine Research Center at the University of Kentucky. This workshop represented an intellectual turning point in racing regulation, in that it marked the formal academic and regulatory acceptance of the concept of limited sensitivity testing for therapeutic medications in the United States.

The HBPA has also tackled the basic scientific problems facing medication control programs. In 1995, the Florida HBPA initiated a chemical synthesis program for equine drug metabolite regulatory analyte standards at the University of Kentucky (see Appendix IV). Additionally, many local HBPAs and the National HBPA under Presidents Bill Walmsley, Rick Hiles, John Roark, and Joe Santanna supported research on developing a scientific basis for regulatory thresholds for therapeutic medications, as set forth in Appendices IV and V.

This research on regulatory thresholds for therapeutic medications was published in the scientific literature, and it attracted the attention of the veterinary research community. One outcome was that in 1998, the *Journal of Veterinary Pharmacology and Therapeutics* requested an overview of HBPA-supported research in this area, and this work was published as an invited scientific review [6].

This research on regulatory thresholds for therapeutic medications was also supported by the Kentucky Racing Commission, the Kentucky Equine Drug Research Council under the able leadership of Commissioners C. Bruce Hundley and Robert G. Stallings, and the dedicated efforts of all members of the Equine Pharmacology, Therapeutics, and Toxicology group at the University of Kentucky. Additionally, it is a pleasure to recognize the ongoing support of the faculty of the Gluck Equine Research Center and its longtime director, Dr. Peter Timoney. Finally, this document also reflects contributions of Dr. Linda Kiesel of Agricultural Communications Services in the College of Agriculture at UK, Ms. Amy Troppmann of the Gluck Equine Research Center, and, most recently, Dr. Wendy Spencer of the Gluck Equine Research Center.

TERMS OF REFERENCE / DISCLAIMER

This 2008 Proposed National Policy on Drug Testing and Therapeutic Medication Regulation is based on and draws heavily from our previous 2001 and 2003 National Horsemen's Benevolent and Protective Association (NHBPA) Proposed National Policies on Drug Testing and Therapeutic Medication Regulation. The information contained herein should not be construed as anything other than a proposed policy with supporting documentation.

Significant portions of the documentation we acquired are not readily available in the public domain. This is because much of the information on medication regulation in the United States is held "in house" and therefore not generally available; for example, the regulatory thresholds in Ohio were communicated to us in the summer of 1999. Some of these thresholds may have changed since then; however, the Ohio authorities have declined requests to update our information. Similar "in house" unpublished regulatory thresholds are also apparently in place in many other jurisdictions, including but not limited to Pennsylvania, California, Kentucky, and Florida.

Given these limitations, much of the information on thresholds presented in this review has been gleaned from racing authority Web sites and from documentation available to us from other sources. This proposed policy represents our best current analysis, but it should be clearly understood that therapeutic medication regulation is an evolving area. It is therefore probable that some of the presented thresholds are in the process of change; we have, to the best of our ability, indicated where we believe this is either likely to occur or actually under way.

Given these circumstances, the information presented in this proposed policy is simply our best current analysis; it should never be taken as an authoritative guide with respect to drug testing and medication regulation in any specific jurisdiction. In such circumstances, horsemen and other industry professionals should always consult with their veterinary advisors or the appropriate regulatory authorities when seeking information or guidance with regards to the specific regulations or regulatory procedures in place in any jurisdiction at any given time.

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1. Executive Summary

The National Horsemen's Benevolent & Protective Association (NHBPA) herein presents its 2008 updated Proposed National Policy on Drug Testing and Therapeutic Medication Regulation for Association of Racing Commissioners International (ARCI) class 1, 2, 3, 4, and 5 substances. This document defines the relevant terms and sets forth the regulatory need and scientific basis for:

1.1 A **ZERO TOLERANCE POLICY** on testing for performance-altering substances that have no legitimate use in horses in training or racing and are not therapeutic medications or endogenous, dietary, or environmental substances. This zero tolerance policy also applies to prohibited practices, including but not limited to administration of milkshakes, erythropoietins, growth hormones, or unregulated shock-wave therapy.

1.2 **THRESHOLDS/REGULATORY LIMITS** for substances recognized by the Racing Medication and Testing Consortium (RMTC), the Association of Racing Commissioners International (ARCI), the American Association of Equine Practitioners (AAEP), or racing jurisdictions as therapeutic medications for the horse. A threshold is a defined concentration of a specified substance, the regulatory analyte, in a defined matrix, usually plasma or urine. The thresholds/regulatory limits presented herein are based on published scientific research and/or thresholds/regulatory limits adopted by RMTC/ARCI or one or more racing or other organizations or jurisdictions.

1.3 **THRESHOLDS / REGULATORY LIMITS** for the following AAEP/RMTC/ARCI therapeutic medications: acepromazine, albuterol, aminocaproic acid, atropine, beclomethasone, betamethasone, buscopan, butorphanol, carbazochrome, cimetidine, clenbuterol, cromolyn, dantrolene, detomidine, dexamethasone, diazepam, diclofenac, dimethylsulfoxide, dipyrone, flunixin, fluoroprednisolone, fluphenazine, furosemide, glycopyrrolate, guaifenesin, hydroxyzine, ibuprofen, isoflupredone, isoxsuprine, ketoprofen, lidocaine, meclofenamic acid, mepivacaine, methocarbamol, methylergonovine, methylprednisolone, naproxen, omeprazole, pentoxifylline, phenylbutazone, phenytoin, prednisolone, prednisone, procaine penicillin, pyrilamine, ranitidine, reserpine, stanozolol, triamcinolone, trichlormethiazide, and xylazine.

1.4 **THRESHOLDS / REGULATORY LIMITS** for endogenous, dietary, or environmental substances that are also ARCI substances, including atropine, benzoylecgonine, boldenone bufotenine, caffeine, hydrocortisone, morphine glucuronides, nandrolone, salicylic acid/salicylates, scopolamine, strychnine, testosterone, and theobromine.

1.5 **SALIX® (LASIX®) CONTROL:** Application of these thresholds/regulatory limits for substances in urine requires that Salix® (furosemide, Lasix) administration be controlled such that urinary dilution does not interfere with testing.

1.6 **WITHDRAWAL TIME GUIDELINES:** The absolute need of racing industry professionals for practical "withdrawal time guidelines" scientifically linked to the relevant specific

thresholds/regulatory limits set forth herein is explicitly recognized. Research to establish and publish the best possible scientific basis for such "withdrawal time guidelines," including scientifically determined and published estimates of the uncertainty associated with each withdrawal time guideline should be a high priority for the industry.

1.7 **BLOOD TESTING** provides a significantly superior scientific basis for the regulation of therapeutic medication. All testing laboratories should have appropriate instrumentation, including Liquid Chromatography Mass Spectrometry- Mass Spectrometry [LC-MS-MS] instrumentation to optimize regulatory practices through application of blood testing.

1.8 **NATIONAL STANDARDS** are proposed for administrative procedures, laboratory accreditation, the reporting of chemical identifications and their quantitative determination, independent analysis and review, with an emphasis on the importance of expert professional review. With regard to the matter of standards, the current emphasis of HBPA-supported research is provision of the Certified Reference Standards and stable isotope internal standards required for accurate quantification of thresholds substances.

1.9 **RESEARCH:** The ongoing development of new therapeutic medications and improved analytical technologies means that the specifics of this policy will continue to evolve with time.

2. Preamble

2.1 **SCOPE OF THE PROPOSED POLICY:** The NHBPA herein presents its 2008 Proposed National Policy on Drug Testing and Therapeutic Medication Regulation for ARCI class 1, 2, 3, 4, and 5 substances.

2.2 **GOAL OF THE PROPOSED POLICY:** The goal of this proposed policy is to integrate medication policies and their regulation across the United States. In approaching this goal, the NHBPA has chosen to build on established regulatory precedent. Established regulatory precedent includes published or, where these have become available, "in house" [unpublished] thresholds or regulatory limits adopted by racing authorities, as set forth in this and previous iterations of this document. This policy again explicitly sets forth the need for national regulatory thresholds and withdrawal time guidelines scientifically linked to the specific regulatory thresholds for defined regulatory analytes and based on published scientific research, as set forth in Section 12.2 and Appendix I.

2.3 **REGULATORY PRECEDENTS FOR THE PROPOSED POLICY:** In presenting this document, the NHBPA recognizes and endorses the approaches first set forth in the long-established Canadian policy of limited sensitivity testing for therapeutic medications, the McKinsey Report (1991) [1], the National Thoroughbred Racing Association Racing Integrity and Drug Testing Task Force report (May 2001) [2], and the ongoing contributions from the RMTC and ARCI. Beyond this, however, this document draws freely on terms, definitions, and specific thresholds/limits/decision levels/regulatory limits (hereinafter called

"thresholds/regulatory limits") presented in the scientific or regulatory literature or already in place in North American racing jurisdictions, including Arizona, Arkansas, California, Colorado, Delaware, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Virginia, Washington, West Virginia, Wyoming, Canada, RMTC, ARCI, and other national and international jurisdictions.

2.4 SCIENTIFIC AND TECHNICAL BASIS FOR THE PROPOSED POLICY: As set forth in this document, standardized national medication rules cannot be put in place without *standardized regulatory thresholds defined as plasma or urinary concentrations of a specified regulatory analyte*, the availability of the appropriate regulatory analyte reference standards, appropriate internal standards, validated analytical methods, and appropriate research bases. In this regard, the National and local HBPAs, in cooperation with other groups, have supported research on the synthesis of the required regulatory analyte reference standards, including stable isotope/deuterated and equine drug metabolite fragment regulatory analyte reference standards; the development of validated analytical methods; and the development of appropriate scientifically determined and published research bases, including withdrawal time guidelines with scientifically defined uncertainties for each of the listed therapeutic medications. The research base for this approach is summarized in the scientific papers that are referenced throughout the text and listed in Appendices VIII and IX.

2.5 ADMINISTRATIVE BASIS FOR THE PROPOSED POLICY: Horses are commonly entered to race at 48 hours prior to post. Where possible, the therapeutic medication policies presented here have been structured, or should optimally be structured, so as to minimize interference with the process of entering horses to race while preserving the health and welfare of the horse.

2.6 DEFINITIONS: Central to any scientific or regulatory process is the precise definition of terms. This document therefore defines the relevant regulatory and scientific terms and sets forth the regulatory need and the best available scientific basis for this policy (superscripts throughout text refer to the definitions presented in Appendix II).

3. Zero Tolerance Policy on Testing for Prohibited Practices and Performance-Altering Substances

3.1 ZERO TOLERANCE POLICY[1] on testing for performance-altering substances[2] that have no legitimate use in horses in training or racing and are not therapeutic medications or endogenous, dietary, or environmental substances. This zero tolerance policy also applies to prohibited practices, including but not limited to administration of milkshakes, erythropoietins, growth hormones, or unregulated shock-wave therapy.

3.2 ZERO TOLERANCE POLICY for performance-altering substances that have no recognized legitimate use in horses in training or racing; for these substances, any quantity detected is violative.

3.3 ZERO TOLERANCE POLICY means, in practice, utilizing the most sensitive testing procedures available that encompass the full scope and sensitivity of modern analytical methods.

3.4 ZERO TOLERANCE POLICY therefore mandates application of the fullest possible range of highly sensitive ELISA tests and instrumental and other screening[3] and confirmation[4] methods.

3.5 ZERO TOLERANCE POLICY for performance-altering substances also mandates vigorous research efforts to develop highly sensitive tests for all performance-altering substances.

3.6 ZERO TOLERANCE POLICY for performance-altering substances, with the application of appropriate penalties, is unequivocally supported and endorsed by the NHBPA and all HBPA affiliates throughout North America.

3.7 Endorsement of this zero tolerance policy approach is based on the requirement that all analytical results and proposed administrative actions have been reviewed by appropriate experts, and this review is especially important for novel identifications[4] "positives." Within the limits of available knowledge and technology, all innocent explanations of the practices or substances in question shall have been rigorously examined and excluded from consideration prior to any regulatory action being taken.

4. Regulation of Therapeutic Medications

4.1 Therapeutic medications[5, 6] are necessary to preserve the health and welfare of horses. The NHBPA recognizes that horses in training, like all athletes, will at times require the administration of certain therapeutic medications to preserve their health.

4.2 The NHBPA specifically recognizes the role of the AAEP, the now forming Association of Equine Racetrack Veterinarians [AERV], the RMTC, and the ARCI in identifying substances as therapeutic medications (see Appendix III). The NHBPA further recognizes, encourages, and supports the AAEP's role in defining appropriate standardized therapeutic dosage

regimens[7] of these therapeutic medications with the primary goal of preserving the health of horses. The AAEP has recently defined standardized therapeutic dosage regimens for therapeutic medications that will serve to guide veterinary practitioners, analytical chemists, pharmacologists, regulators, and other industry professionals across the nation (Appendix III), and these AAEP standardized therapeutic dosage regimens are included in this document courtesy of Dr. Rick Arthur and the AAEP.

4.3. A ZERO TOLERANCE POLICY, as established and set forth above for performance-altering substances is, by definition, inappropriate for use in the regulation of therapeutic medication. Zero tolerance policy testing inevitably leads to the detection of insignificant trace concentrations[8] of therapeutic medications long after their therapeutic effects are over. Additionally, testing continually increases in sensitivity as analytical methods improve. ***As such, a zero tolerance policy is completely inappropriate for application to testing for therapeutic medications or as a basis for a national medication regulation policy since zero tolerance testing is, by definition, an ever-changing standard.***

5. The Problem: Ramifications of a Zero Tolerance Policy

5.1 In the absence of national standards, zero tolerance policy testing for ineffective traces of therapeutic medications or endogenous, dietary, or environmental substances [9] is a significant problem that causes damage to the sport of racing in the following ways.

5.2 First and foremost, a zero tolerance policy damages the health and welfare of horses through inhibition or prohibition of the administration of therapeutic medications to horses, thereby interfering with proper veterinary care and humane preservation of the health of racing horses.

5.3 Second, a zero tolerance policy damages the reputation of racing through media stories that are inaccurate or incomplete and that improperly and unnecessarily harm public confidence in the integrity of racing.

5.4 Third, a zero tolerance policy damages the reputations of individual trainers by associating them in the minds of owners and the racing public with supposedly improper medication practices.

5.5 Fourth, a zero tolerance policy causes damage to the reputations of affected owners and, by extension, all owners, thereby discouraging their participation in racing.

5.6 Fifth, under a zero tolerance policy, individual regulators may utilize tests of differing sensitivities for therapeutic medications, resulting in industry-wide confusion and inequitable penalties, further exacerbating these problems.

6. The Solution: National Standards andThresholds / Regulatory Limits for Therapeutic Medications and Endogenous, Dietary, and Environmental Substances

6.1 The solution is for racing to adopt uniform national testing standards, more specifically national thresholds/regulatory limits[10] for therapeutic medications and endogenous, dietary, and environmental substances, based on published research and thresholds/regulatory limits already in place in Arizona, Arkansas, California, Colorado, Delaware, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Virginia, Washington, West Virginia, Wyoming, Canada, and RMTC/ARCI and other national and international racing jurisdictions or bodies.

6.2 As set forth below, the NHBPA has supported research in these areas and has contributed to the synthesis and availability of a substantial number (> 36) of specific equine regulatory analyte reference standards[11] and stable isotope internal standards, which standards are an absolute requirement for implementation of regulatory thresholds through quantification of regulatory analyte concentrations present in or recovered from horse plasma or urine (see Appendix IV). The NHBPA therefore proposes the following uniform national thresholds /regulatory limits and associated withdrawal time guidelines for various ARCI class 1, 2, 3, 4, and 5 substances. [3, 4, 5, 6, 7]

6.3 **WITHDRAWAL TIME GUIDELINES**[12]: Thresholds/regulatory limits are defined *concentrations*[13] of specified regulatory analytes in or recovered from biological fluids above which concentrations regulatory processes may be initiated. As a practical matter, however, horsemen need "withdrawal time guidelines" scientifically linked[14] to the specific defined thresholds/regulatory limits set forth hereafter. Current availability of published withdrawal time guideline information scientifically linked to defined regulatory thresholds is very limited; this area is therefore the highest priority for research.

7. National Thresholds/Regulatory Limits for Therapeutic Medications

7.1 ARCI Class 2 Therapeutic Medications

Thresholds/regulatory limits in place in North America for two AAEP/RMTC/ARCI approved ARCI class 2 local anesthetics, lidocaine and mepivacaine, are presented below. Each of these thresholds/regulatory limits is in urine and is well documented in published research supported in part by the National and local Horsemen's Benevolent & Protective Associations (see Appendix V). No withdrawal time guidelines for these local anesthetics linked to these thresholds/regulatory limits are currently available. To prevent the improper use of synergistic combinations of local anesthetics or other ARCI class 2 substances, these thresholds/regulatory limits will not apply if more than one pharmacologically related ARCI substance is detected. [8, 9, 10] Other published regulatory

thresholds for ARCI class 2 therapeutic medications include a regulatory threshold for bupivacaine [8] in place in two states, Ohio and Washington.

7.1.1 LIDOCAINE (local anesthetic)

REGULATORY ANALYTE [15]: **3-hydroxylidocaine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

Ohio (1999*) and Washington have adopted this threshold/regulatory limit for lidocaine, an ARCI class 2 therapeutic medication. This threshold/regulatory limit is well supported by published research. [9, 10]. Both Louisiana and Oklahoma, however, have adopted a threshold/regulatory limit of 25 ng/ml in urine. In the horse, the regulatory analyte, 3-hydroxylidocaine, is recovered from the major urinary metabolite of lidocaine, 3-hydroxylidocaine glucuronide. Because of its widespread use as a local anesthetic additive in topical medications, in Louisiana lidocaine is classified as an environmental substance. Louisiana has also adopted a plasma/serum threshold for lidocaine of < 1 ng/ml. Lidocaine is an RMTC priority for regulatory threshold and withdrawal time guideline development, and certified reference standards of the regulatory analyte, 3-hydroxylidocaine, and the corresponding stable isotope reference standard, deuterated 3-hydroxylidocaine, have been synthesized and are available to industry researchers and racing chemists, courtesy of HBPA-supported research [6, 8, Appendices IV and V].

AAEP-Standardized Therapeutic Dosage Regimen for Lidocaine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
UP TO 200 MG	SQ	ONCE	LOCAL ANESTHETIC	48 HRS

TOBA (Thoroughbred Owners and Breeders Association) Testing:

For lidocaine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is 3-hydroxylidocaine.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of lidocaine at the above threshold/regulatory limit are available at this time.

NOTE: Ohio threshold/regulatory limits presented in this document are taken from a 1999 communication, and some of these thresholds/regulatory limits may have changed. Requests for information on current threshold/regulatory limits received no response from the Ohio State Racing Commission.

7.1.2 MEPIVACAINE (local anesthetic)

REGULATORY ANALYTE: **3-hydroxymepivacaine**

Threshold/Regulatory Limit: **25 ng/ml, from /in urine**

Louisiana has adopted this threshold/regulatory limit of 25 ng/ml in urine. California, Washington, and New Mexico have adopted a 10 ng/ml threshold/regulatory limit for mepivacaine, an ARCI class 2 therapeutic medication. This threshold/regulatory limit is well supported by published research. [11, 12] In the horse, the regulatory analyte, 3-hydroxymepivacaine, is recovered from the major urinary metabolite of mepivacaine, 3-hydroxymepivacaine glucuronide. Mepivacaine is also an RMTC priority for regulatory threshold and withdrawal time guideline development and certified reference standards of the regulatory analyte, 3-hydroxmepivacaine, and the corresponding stable isotope internal standard, deuterated 3-hydroxymepivacaine have been synthesized and are available to industry researchers and racing chemists, courtesy of HBPA-supported research [6, 8, Appendices IV and V]

AAEP-Standardized Therapeutic Dosage Regimen for Mepivacaine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
UP TO 50 MG	SQ	ONCE	LOCAL ANESTHETIC	48 HRS

TOBA Testing:

For mepivacaine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is 3-hydroxymepivacaine.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of mepivacaine at the above threshold/regulatory limit are available at this time.

7.1.3 Other Published Regulatory Thresholds for ARCI Class 2 Therapeutic Medications:

7.1.3.1 BUPIVACAINE (local anesthetic)

REGULATORY ANALYTE: **3-hydroxybupivacaine**

Threshold/Regulatory Limit: **5 ng/ml, from/in urine**

Ohio (1999) and Washington have adopted this threshold/regulatory limit for bupivacaine, an ARCI class 2 therapeutic medication. This threshold/

regulatory limit is well supported by published research, and a certified reference standard of the regulatory analyte, 3-hydroxybupivacaine, is available to industry researchers and racing chemists courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

TOBA Testing:

For bupivacaine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is 3- hydroxybupivacaine.

Standardized Therapeutic Dosage Regimen for Bupivicaine:

No standardized dosage has been recommended by either AAEP or RMTC.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of bupivacaine at the above threshold/regulatory limit are available at this time.

7.1.4 Four other ARCI class 2 substances, namely **diazepam** (sedative), **fluphenazine** (long-acting tranquilizer), **hydroxyzine** (anti-histaminic), and **reserpine** (long-acting tranquilizer), are AAEP-/RMTC-/ARCI-recognized therapeutic medications (see Appendix III) for which no defined regulatory analyte, regulatory matrix (blood or urine), published thresholds/regulatory limits, or withdrawal time guidelines are currently available.

7.1.4.1 DIAZEPAM

AAEP/RMTC recommends the following therapeutic dosage regimen for diazepam:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
20-30 MG	IV	SID	TRANQUILIZER/ SEDATIVE	72-120 HOURS

TOBA Testing:

For diazepam, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is/are nordiazepam, oxazepam and temazepam.

7.1.4.2 FLUPHENAZINE

AAEP/RMTC recommends the following therapeutic dosage regimen for fluphenazine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
10-30 MG	IM	SID EVERY 1-2 WEEKS	LONG-ACTING TRANQUILIZER	7+ DAYS

TOBA Testing:

For fluphenazine, the TOBA-suggested screening method is LC/MS, and the suggested minimum concentration is 500 pg/ml in plasma. The analyte detected is fluphenazine.

A certified reference standard of a candidate regulatory analyte for fluphenazine, hydroxyfluphenazine, has been synthesized and made available to industry researchers and racing chemists, courtesy of HBPA-supported research [6, 8, Appendices IV and V].

7.1.4.3 HYDROXYZINE

AAEP/RMTC recommends the following therapeutic dosage regimen for hydroxyzine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
250-500 MG	PO	BID	CHRONIC URTICARIA	72 HOURS

TOBA Testing:

No suggested criteria.

7.1.4.4 RESERPINE

AAEP/RMTC recommends the following therapeutic dosage regimen for reserpine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
2.5 MG	IM	ONCE EVERY 2-3 WEEKS	LONG-ACTING TRANQUILIZER	7+ DAYS

TOBA Testing:

For reserpine, the TOBA-suggested screening method is LC/MS, and the suggested minimum concentration is 50 pg/ml in plasma. The analyte detected is reserpine.

7.2 ARCI Class 3 Therapeutic Medications

Thresholds/regulatory limits in place in North America for seven AAEP/RMTC/ARCI-approved ARCI class 3 therapeutic medications are presented below. With the exception of clenbuterol, all of these thresholds/regulatory limits are in urine. Also with the possible exception of clenbuterol, no scientifically determined and published withdrawal time guidelines linked to these thresholds/regulatory limits are available.

Research on blood testing for clenbuterol under the aegis of the California Horse Racing Board [CHRB] and earlier research supported by the National and several local Horsemen's Benevolent & Protective Associations have presented data supporting a threshold/regulatory limit of 25 picograms/ml in blood serum for clenbuterol. [13] This research is largely consistent with research from Ohio, New York, and Pennsylvania [14, 15]. With regard to the other listed ARCI class 3 substances, scientifically determined and published withdrawal time guidelines linked to the indicated thresholds/regulatory limits are needed for either the presented urinary thresholds/regulatory limits or their equivalent thresholds /regulatory limits in blood plasma or serum. Other regulatory thresholds for ARCI class 3 therapeutic medications include regulatory thresholds for three other ARCI class 3 medications, pentazocine, promazine, and terbutaline, in place in Ohio in 1999.

One ARCI class 3 AAEP/RMTC/ARCI therapeutic medication, atropine, is also a dietary/environmental substance, and as such, atropine is listed in Section 9, "Policy on Endogenous, Dietary, and Environmental Substances."

To prevent the improper use of synergistic combinations of ARCI class 3 therapeutic medications, these thresholds/regulatory limits will not apply if more than one pharmacologically related ARCI substance is detected.

7.2.1 ACEPROMAZINE (tranquilizer)

REGULATORY ANALYTE: **2-(1-hydroxyethyl) promazine sulfoxide (HEPS)**

Threshold/Regulatory Limit: **25 ng/ml, from/in urine**

California, Louisiana, New Mexico, and Washington have adopted this threshold/regulatory limit for acepromazine, an ARCI class 3 therapeutic medication. In the horse, the regulatory analyte, 2-(1-hydroxyethyl) promazine sulfoxide (HEPS), is recovered from the major urinary metabolite of acepromazine, 2-(1-hydroxyethyl) promazine sulfoxide (HEPS) glucuronide. A certified reference standard of the regulatory analyte 2-(1-hydroxyethyl) promazine sulfoxide and the corresponding internal standard, deuterated 2-(1-hydroxyethyl) promazine sulfoxide, have been synthesized and are available to industry researchers and racing chemists, courtesy of HBPA-supported research. [5, 6, 8, Appendices IV and V].

AAEP-Standardized Therapeutic Dosage Regimen for Acepromazine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
15 MG	IV	SID	TRANQUILIZER	48 HRS (72-24 HRS)

TOBA Testing:

For acepromazine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is 2-(1-hydroxyethyl) promazine sulfoxide .

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of acepromazine at the above threshold/regulatory limit are available at this time.

NOTE: At this time, many racing authorities have no published recommended regulatory threshold for acepromazine, and acepromazine is an RMTC priority for developing a regulatory threshold and withdrawal time guidelines. Lack of an RMTC threshold for acepromazine has recently (late 2007) resulted in suspension of regulatory action on a number of low (<25 ng/ml) concentration urinary acepromazine identifications in Florida racing. At press time, there are indications that Florida is considering a 10 ng per milliliter threshold/regulatory limit for acepromazine in urine [Personal communication, T. Tobin].

7.2.2 ALBUTEROL (bronchodilator)

REGULATORY ANALYTE: **Albuterol**

Threshold/Regulatory Limit: **1 ng/ml, from/in urine:**

California, New Mexico, and Washington have adopted this threshold/regulatory limit for albuterol, an ARCI class 3 therapeutic medication. The threshold/ regulatory limit for albuterol in one unidentified American jurisdiction is reportedly 2 ng/ml in urine [2], while it is 5 ng/ml in urine in Louisiana. Two racing commissions, namely Louisiana and Oklahoma, have also adopted plasma/serum thresholds for albuterol of 1 ng/ml.

AAEP-Standardized Therapeutic Dosage Regimen for Albuterol:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
6 PUFFS	INHALER (MDI)	BID	BRONCHODILATOR	24 HRS

TOBA Testing:

For albuterol, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 2 ng/ml in urine. The analyte detected is albuterol.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of albuterol at the above threshold/regulatory limit are available at this time.

7.2.3 BUTORPHANOL (analgesic)

REGULATORY ANALYTE: **Butorphanol**

Threshold/Regulatory Limit: **10 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for butorphanol, an ARCI class 3 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Butorphanol:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-10 MG	IV	ONCE	TRANQUILIZER	48 HRS

TOBA Testing:

For butorphanol, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration in urine is 20 ng/ml in urine. The analyte detected is butorphanol.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of butorphanol at the above threshold/regulatory limit are available at this time.

7.2.4 CLENBUTEROL (bronchodilator)

REGULATORY ANALYTE: **Clenbuterol**

Thresholds/Regulatory Limits: **25 pg/ml, from/in plasma/serum**

This 25 pg/ml plasma/serum threshold/regulatory limit for clenbuterol is in place in California, Kentucky, and Washington and is supported by CHRB and the University of California-Davis "in house" research on about 20 horses in training. This regulatory threshold is generally consistent with published research [13] and in-house research (Ohio, New York) and is consistent with Canadian policy and recently published research from the University of Pennsylvania. [14, 15] Louisiana and Oklahoma have adopted plasma/serum thresholds of 0.5 and 1 ng/ml, respectively. California and New Mexico have also established threshold/regulatory limits for clenbuterol in urine of 5 ng/ml, while Louisiana maintains a threshold of 15 ng/ml in urine. As of January 1, 2008, the Pennsylvania State Horse Racing Commission (PASHRC) has implemented a 24-hour withdrawal time for clenbuterol, reportedly [Pennsylvania HBPA] with a 125 pg/ml plasma threshold.

AAEP-Standardized Therapeutic Dosage Regimen for Clenbuterol:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
0.8 MCG/KG	PO	BID	BRONCHODILATOR	96 HRS*

TOBA Testing:

For clenbuterol, the TOBA-suggested screening method is LC/MS in plasma or ELISA in urine, and the suggested minimum concentration is 20 pg/ml in plasma and 1 ng/ml in urine and the analyte detected is clenbuterol.

Withdrawal Time Guideline:

At this time, no scientifically determined and published withdrawal time guideline linked to the 25 pg/ml plasma/serum threshold for clenbuterol is reported in the scientific literature; however, California suggests a 96-hour withdrawal time associated with this regulatory threshold, with no defined level of uncertainty.

Deuterated clenbuterol (clenbuterol D_9) for use as an internal standard has been synthesized and is available to industry researchers and racing chemists, courtesy of HBPA-supported research [6, 8, Appendices IV and V].

7.2.5 GLYCOPYRROLATE (bronchodilator)

REGULATORY ANALYTE: **Glycopyrrolate**

Threshold/Regulatory Limit: **5 ng/ml, from/in urine**

Ohio has adopted this threshold/regulatory limit for glycopyrrolate, an ARCI class 3 therapeutic medication.

No AAEP-standardized therapeutic dosage regimen is currently available for glycopyrrolate.

In an unpublished document communicated in 2005, the RMTC Advisory Committee recommends the following dosage regimen for glycopyrrolate:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
1 MG	IV or IM	SID		

TOBA Testing:

For glycopyrrolate, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is glycopyrrolate.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of glycopyrrolate at the above threshold/regulatory limit are available at this time.

7.2.6 PROCAINE (local anesthetic)

REGULATORY ANALYTE: **Procaine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

Ohio (1999) and Louisiana have adopted a 50 ng/ml urinary threshold/regulatory limit for procaine, an ARCI class 3 therapeutic medication, and this threshold was, at one time, in place in Kentucky. This threshold/regulatory limit is well supported by published research [16]. Washington, California, and New Mexico have respectively adopted threshold/regulatory limits of 25, 10, and 10 ng/ml in urine. Louisiana and Oklahoma also recognize plasma threshold/regulatory limits for procaine of 5 ng/ml and 25 ng/ml, respectively.

AAEP-Standardized Therapeutic Dosage Regimen for Procaine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
20 MG/ML PROCAINE (≈30 ML, 9,000,000 units)	IM	BID	PROCAINE LOCAL ANESTHETIC (PPG ANTIBIOTIC)	48 HRS

TOBA Testing:

For procaine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is procaine.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of procaine at any of the above urinary threshold/regulatory limits are available at this time. Deuterated procaine (D_9 procaine) for use as an internal standard and quantitative analytical work has been synthesized and is available to industry researchers and racing chemists, courtesy of HBPA-supported research [6, 8, Appendices IV and V].

NOTE: Procaine penicillin is an important therapeutic medication in racing horses. Development of a national blood/plasma threshold/regulatory limit for this substance would likely permit its more therapeutically effective use closer to post than the current urine threshold/regulatory limit in place. Currently in place blood/plasma thresholds/regulatory limits include 25 ng/ml in plasma in Oklahoma and Canada, 20 ng/ml in plasma in Pennsylvania, and 5 ng/ml in plasma in Louisiana with rigorous reporting requirements concerning the pre-race administration of procaine penicillin. [17]

7.2.7 PYRILAMINE (anti-histaminic)

REGULATORY ANALYTE: **O-desmethylpyrilamine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

Ohio (1999) adopted a Thin Layer Chromatography threshold/regulatory limit for pyrilamine, an ARCI class 3 therapeutic medication, estimated at 50 ng/ml. Washington has also adopted this urinary threshold/regulatory limit. Oklahoma has adopted a plasma/serum threshold for pyrilamine of 50 ng/ml. The regulatory analyte, O-desmethylpyrilamine, is a major urinary metabolite fragment of pyrilamine in the horse, and a certified reference standard of O-desmethylpyrilamine is available to industry researchers and scientists, courtesy of HBPA supported research. [5, 6, 18, 19, 20]. More recently, it appears that a regulatory threshold in plasma will be developed for pyrilamine, and an appropriate stable isotope internal

standard ($C_{13}D_3$ Pyrilamine) has been synthesized, courtesy of HBPA-supported research [5, 6, 18, 19, 20].

No AAEP-standardized therapeutic dosage regimen is currently available for pyrilamine.

In an unpublished document, the RMTC Advisory Committee recommends the following dosage regimen for pyrilamine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
200-400 MG	PO or IM	SID-BID		

TOBA Testing:

For pyrilamine, the TOBA-suggested screening method is ELISA. and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is O-desmethylpyrilamine.

Withdrawal Time Guideline:

No scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of pyrilamine at the above threshold/regulatory limit are available at this time.

NOTE: Pyrilamine is an oral medication, it appears to be stable in the environment, the dose is large, the plasma half-life is long, and ELISA tests are highly sensitive; as such, pyrilamine is an agent for which "traces" have been reported detected for up to 14 days after the last administration. Pyrilamine is an RMTC priority medication for developing threshold and withdrawal time guidelines , and stable isotope-labeled pyrilamine has recently been synthesized as an internal standard for plasma threshold quantitation of pyrilamine, as set forth above.

7.2.8 Other Regulatory Thresholds for ARCI Class 3 Therapeutic Medications:

7.2.8.1 PENTAZOCINE (analgesic)

<u>REGULATORY ANALYTE</u>: **Pentazocine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for pentazocine, an ARCI class 3 therapeutic medication.

Standardized Therapeutic Dosage Regimen for Pentazocine:

No AAEP- or ARCI/RMTC-standardized therapeutic dosage regimen is currently available for pentazocine.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of pentazocine at the above threshold/regulatory limit are available at this time.

7.2.8.2 PROMAZINE (tranquilizer)

REGULATORY ANALYTE: **3-hydroxpromazine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for promazine, an ARCI class 3 therapeutic medication. Three other commissions, Washington, California, and New Mexico, have adopted a threshold of 25 ng/ml urine.

AAEP-Standardized Therapeutic Dosage Regimen for Promazine:

No AAEP- or ARCI/RMTC-standardized therapeutic dosage regimen is currently available for promazine.

TOBA Testing:

For promazine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is 3-hydroxpromazine

Withdrawal Time Guideline:

No scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of promazine at the above threshold/regulatory limit are available at this time. The regulatory analyte, 3-hydroxypromazine, a major urinary metabolite fragment of promazine in the horse, has been synthesized, and a certified reference standard of this regulatory analyte is available to racing chemists and researchers, courtesy of HBPA-supported research. [5, 6, Appendices IV and V].

7.2.8.3 TERBUTALINE (bronchodilator)

REGULATORY ANALYTE: **Terbutaline**

Threshold/Regulatory Limit: **10 ng/ml, from/in urine**

Ohio (1999) has adopted this threshold/regulatory limit for terbutaline, an ARCI class 3 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Terbutaline:

No AAEP- or ARCI/RMTC-standardized therapeutic dosage regimen is currently available for terbutaline.

TOBA Testing:

For terbutaline, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is terbutaline.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of terbutaline at the above threshold/regulatory limit are available at this time.

7.2.9 Two other RMTC/ARCI class 3 therapeutic medications, namely detomidine (analgesic/sedative) and xylazine (analgesic/sedative), are recognized AAEP/RMTC/ARCI therapeutic medications (see Appendix III) for which for which the AAEP has presented the following standardized therapeutic dosage regimens, but no published thresholds /regulatory limits or scientifically determined and published withdrawal time guidelines are currently available.

7.2.9.1 DETOMIDINE

REGULATORY ANALYTE: **Carboxy-detomidine**

Threshold/Regulatory Limit: **None**

No published regulatory threshold for detomidine or a regulatory analyte of detomidine is available or identifiable and detomidine alcohol is also a suggested urinary regulatory analyte.

AAEP-Standardized Therapeutic Dosage Regimen for Detomidine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-10 MG	IV, IM	ONCE	TRANQUILIZER	48 HRS

TOBA Testing:

For detomidine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is detomidine alcohol.

The regulatory analyte, COOH-detomidine, a major urinary metabolite fragment of detomidine in the horse, has been synthesized, and a certified reference standard and the corresponding deuterated internal standard, D4 carboxydetomidine, are available to racing chemists and researchers, courtesy of HBPA-supported research [5, 6, Appendices IV and V].

7.2.9.2 XYLAZINE

REGULATORY ANALYTE: **None identified**
Threshold/Regulatory Limit: **None**

No published regulatory threshold for xylazine or a regulatory analyte of xylazine is available or identifiable.

AAEP-Standardized Therapeutic Dosage Regimen for Xylazine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
100-400 MG	IV, IM	SID	TRANQUILIZER	48 HRS

TOBA Testing:
No suggested criteria.

NOTE: As set forth above, at this time racing authorities have no published or available recommended regulatory thresholds for detomidine or xylazine, and detomidine is an RMTC priority for developing regulatory threshold and withdrawal time guidelines.

7.3 ARCI Class 4 Therapeutic Medications

ARCI class 4 substances have less ability to influence the performance of horses, and many are recognized therapeutic medications. Many are also readily detected and regulated in blood as well as urine.

Because many of these substances have been readily detectable for many years, most jurisdictions had long-established regulatory policies, and horsemen are familiar with the locally effective withdrawal times. Beyond this, in some jurisdictions, certain of these substances are therapeutic medications whose administration on race day has been approved by rule or statute.

At least part of the reason that certain of these substances have been approved by rule, statute, or regulatory limit as race day medications has been the considerable technical difficulty in establishing realistic "no race day medication" thresholds/regulatory limits along with the associated withdrawal time guidelines for these agents, as set forth in detail in 7.3.5: Flunixin, 7.3.11: Phenylbutazone, and in Appendix 1 below.

This section of the medication policy recognizes these long-established regulatory precedents for ARCI class 4 therapeutic medications and simply lists regulatory policies and

thresholds/regulatory limits currently in place and, where appropriate, recognizes the RMTC/ARCI regulatory threshold/withdrawal time guideline.

Thresholds/regulatory limits in place in North America for 14 AAEP-/RMTC-/ARCI-approved ARCI class 4 therapeutic medications are presented below. Eight other published regulatory thresholds for ARCI class 4 medications have been approved in various jurisdictions. Four ARCI class 4 AAEP/RMTC/ARCI therapeutic medications, boldenone, hydrocortisone, nandrolone, and testosterone, are also endogenous substances and as such are listed in Section 9, "Policy on Endogenous, Dietary, and Environmental Substances."

7.3.1 BETAMETHASONE (Steroidal anti-inflammatory)

REGULATORY ANALYTE: **Betamethasone**
Threshold/Regulatory Limit: **60 ng/ml, from/in plasma**

Ohio (1999) adopted this threshold/regulatory limit for betamethasone, an ARCI class 4 therapeutic medication. and this threshold/regulatory limit was also in place in one other state.

AAEP-Standardized Therapeutic Dosage Regimen for Betamethasone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
6-30 MG	IA	ONCE	STEROIDAL ANTI-INFLAMMATORY	48 HRS

TOBA Testing:

For betamethasone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is betamethasone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of betamethasone at the above threshold/regulatory limit are available at this time.

7.3.2 DANTROLENE (muscle relaxant)

REGULATORY ANALYTE: **Dantrolene**
Threshold/Regulatory Limit: **100 ng/ml, from/in plasma/serum**

Ohio (1999) adopted this threshold/regulatory limit for dantrolene, an ARCI class 4 therapeutic medication, and this threshold/regulatory limit is also in place in Oklahoma.

AAEP-Standardized Therapeutic Dosage Regimen for Dantrolene:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
300-500 MG	PO	SID	EXERTIONAL MYSOSITIS	48 HRS

TOBA Testing:

For dantrolene, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 100 ng/ml in urine. Tthe analytes detected are dantrolene + 5-hydroxydantrolene.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of dantrolene at the above threshold/regulatory limit are available at this time.

7.3.3 DEXAMETHASONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Dexamethasone**

Threshold/Regulatory Limit: **60 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for dexamethasone, an ARCI class 4 therapeutic medication. Louisiana has adopted a threshold/regulatory limit of 100 ng/ml in urine. The United States Equestrian Federation (USEF) has established a plasma/serum threshold of 3 ng/ml for dexamethasone.

AAEP-Standardized Therapeutic Dosage Regimen for Dexamethasone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
5-40 MG	IV, PO, IM	SID	STEROIDAL ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

For dexamethasone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is dexamethasone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of dexamethasone at the above threshold/regulatory limit are available at this time.

7.3.4 DICLOFENAC (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Diclofenac**

Threshold/Regulatory Limit: **5 ng/ml, from/in plasma/serum**

Kentucky, Oklahoma, and the USEF have adopted this threshold/regulatory limit for diclofenac, an ARCI class 4 therapeutic medication, and this threshold is supported by published research [25]. Louisiana also recognized a 5 ng/ml plasma/serum threshold for diclofenac as of August 2007 but has since apparently adopted a zero tolerance policy for this medication.

No AAEP- or ARCI-/RMTC- standardized therapeutic dosage regimen is currently available for diclofenac.

USEF-recommended maximum dosage per pound of body weight for diclofenac is:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
5 INCH RIBBON, ½ INCH THICK	TOPICAL	2 DOSES PER DAY, 12 HRS APART		12 HRS

TOBA Testing:

For diclofenac, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 100 ng/ml in urine. The analyte detected is diclofenac.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of diclofenac at the above threshold/regulatory limit is available at this time.

7.3.5 DIPYRONE (non-steroidal anti-inflammatory, muscle relaxant)

REGULATORY ANALYTE: **Dipyrone**

Threshold/Regulatory Limit: **1 µg/ml, from/in plasma/serum**

Oklahoma has adopted this threshold/regulatory limit for dipyrone, an ARCI class 4 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Dipyrone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
5-10 GM	IV	SID	ANTI-PYRETIC SPASMOLYTIC	72 HRS

TOBA Testing:

For dipyrone, the TOBA-suggested screening method is TLC, and the suggested minimum concentration is 100 ng/ml in urine. The analyte detected is 4-methylaminoanitpyrine.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of dipyrone at the above threshold/regulatory limit are available at this time.

7.3.6 FLUNIXIN (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Flunixin**

Threshold/Regulatory Limit: **50 ng/ml, from/in plasma/serum**

The California Horse Racing Board (CHRB) regulatory threshold for flunixin based on "in house" determinations on a significant number of horses in training is 50 ng/ml in plasma, with a stated withdrawal time guideline of 24 hours. As of January 2008, the published RMTC/ARCI regulatory threshold was 20 ng/ml in plasma, with a stated withdrawal time guideline of 24 hours, with no defined uncertainty. The thresholds/regulatory limits recognized on the Web sites by the individual racing authorities in plasma/serum are: 1,000 ng/ml for Idaho, New Mexico, and the USEF; 500 ng/ml for Colorado; 250 ng/ml for Oklahoma; 50 ng/ml for Louisiana; 25 ng/ml for Oregon; 20 ng/ml for Arkansas, Illinois, Indiana Iowa, Kansas, Kentucky, Maryland, Minnesota, Virginia, and Washington; and 10 ng/ml for Pennsylvania. Louisiana also recognizes a subthreshold[10] for flunixin of 2 ng/ml in plasma/serum.

AAEP-Standardized Therapeutic Dosage Regimen for Flunixin:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
250-500 MG	IV	SID	NSAID	24 HRS

TOBA Testing:

For flunixin, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in plasma. The analyte detected is flunixin.

Withdrawal Time Guideline:

To our knowledge, other than as set forth above for California, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of flunixin at the above thresholds/regulatory limits are available at this time. Deuterated flunixin (D_3 Flunixin) for use as an internal standard in quantitative analytical work has recently been synthesized and made available to racing chemists and researchers, courtesy of HBPA-supported research [6, 8,

Appendices IV and V].

Comment: In a racing context, flunixin should not be tested for or regulated in urine. Flunixin is administered at half gram doses per day to horses, is excreted in the urine, and appears to be quite stable in the environment. In Rio de Janeiro, recent (circa 2003) introduction of a highly sensitive urinary test for flunixin resulted in horsemen being essentially unable to bring horses free of urinary flunixin metabolites to post; a reasonable regulatory threshold for flunixin has since apparently been introduced in Rio de Janeiro racing. [Personal communication to T. Tobin]

NOTE: At press time, the RMTC is scheduled to present an official RMTC analysis of available flunixin research, presumably including a re-adjusted RMTC-recommended flunixin threshold scientifically linked to a 24-hour withdrawal time guideline.

7.3.7 ISOFLUPREDONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Isoflupredone**
Threshold/Regulatory Limit: **60 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for isoflupredone, an ARCI class 4 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Isoflupredone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
10-20 MG	IA, IM	ONCE	STEROIDAL INFLAMMATORY	48 HRS

TOBA Testing:

For isoflupredone, the TOBA-suggested screening method is ELISA and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is isoflupredone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of isoflupredone at the above threshold/regulatory limit are available at this time.

7.3.8 ISOXSUPRINE (vasodilator)

REGULATORY ANALYTE: **Isoxsuprine**
Threshold/Regulatory Limit: **1,000 ng/ml, from/in urine**

Ohio (1999) and Illinois have adopted this threshold/regulatory limit for isoxsuprine, an ARCI class 4 therapeutic medication. This threshold/regulatory limit is supported by Canadian research [21].

AAEP-Standardized Therapeutic Dosage Regimen for Isoxsuprine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
200-400 MG	PO	BID	PERIPHERAL VASODILATOR	48 HRS

TOBA Testing:

For isoxsuprine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is isoxsuprine.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of isoxsuprine at the above threshold/regulatory limit are available at this time.

NOTE: Isoxsuprine is an oral medication, the dose is large, the plasma half-life may be long, isoxsuprine is chemically stable in the environment, the ELISA test is highly sensitive, and isoxsuprine glucuronides are efficiently excreted at very high concentrations in equine urine; as such, isoxsuprine is *notorious* as an agent for which traces have been reported detected for long periods (months) after the last administration, most likely associated with its persistence in equine environments and resulting in inadvertent re-exposure. These circumstances have recently (2002) been explicitly recognized by Australian regulatory authorities in the Mistegic matter [22] and also by a relatively recent rule change in Illinois.

7.3.9 KETOPROFEN (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Ketoprofen**

Thresholds/Regulatory Limits: **10 ng/ml, from/in plasma**

The RMTC/ARCI and Arkansas, California, Colorado, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Minnesota, Oregon, Washington, and Ohio (2004) have adopted a 10 ng/ml threshold/regulatory limit for ketoprofen, an ARCI class 4 therapeutic medication. Three other authorities, New Mexico, Oklahoma, and the USEF have adopted plasma threshold/regulatory limits of 50 ng/ml, 100 ng/ml, and 250 ng/ml, respectively. Louisiana has also adopted a subthreshold level for ketoprofen of 0.5 ng/ml in plasma/serum.

AAEP-Standardized Therapeutic Dosage Regimen for Ketaprofen:

DOSAGE	ROUTE4	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
1000 MG	IV	SID	NSAID	24 HRS

TOBA Testing:

For ketoprofen, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 10 ng/ml in plasma and the analyte detected is ketoprofen.

Withdrawal Time Guideline:

The regulatory threshold of 10 ng/ml in plasma is considered a 24-hour withdrawal time threshold and is also the official RMTC/ARCI threshold. This threshold/withdrawal time relationship is, at this time, not supported by published research, and there is no defined level of uncertainty associated with this withdrawal time. Deuterated ketoprofen (D_3 Ketoprofen) for use as an internal standard in quantitative analytical work has recently been synthesized and made available to racing chemists and research scientists, courtesy of HBPA- and Kentucky-supported research [6, 8, Appendices IV and V].

7.3.10 METHOCARBAMOL (muscle relaxant)

REGULATORY ANALYTE: **Methocarbamol**

Threshold/Regulatory Limit: **1,000 ng/ml, from/in plasma**

Ohio (1999) and Oklahoma have adopted this threshold/regulatory limit for methocarbamol, an ARCI class 4 therapeutic medication, and this threshold/regulatory limit is also under review in at least one other state, although there are suggestions that this may not be the current regulatory threshold in Ohio. The USEF has adopted a threshold/regulatory limit of 4,000 ng/ml methocarbamol in plasma/serum.

AAEP-Standardized Therapeutic Dosage Regimen for Methocarbamol:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-5 GM	IV	SID, BID	CENTRALLY ACTING MUSCLE RELAXATION	24 HRS
5-20 GM	PO	BID, TID		48 HRS

TOBA Testing:

For methocarbamol the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is methocarbamol.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of methocarbamol at the above threshold/regulatory limit are available at this time. Deuterated methocarbamol (D_4 methocarbamol) for use as an internal standard in quantitative analytical work has recently been synthesized and made available to racing chemists and researchers, courtesy of HBPA- and Kentucky-supported research. [6, 8, Appendices IV and V].

NOTE: The daily dose of methocarbamol is very large (see above oral dose), and as such, methocarbamol is very readily detected by analytical chemists; methocarbamol is therefore a priority for RMTC to develop regulatory threshold and withdrawal time guidelines.

7.3.11 METHYLPREDNISOLONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Methylprednisolone**

Regulatory Limit: **1,000 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for methylprednisolone, an ARCI class 4 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Methylprednisolone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
40-200 MG	IA/IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	48 HRS

TOBA Testing:

For methylprednisolone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is methylprednisolone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of methylprednisolone at the above threshold/regulatory limit are available at this time.

NOTE: Detection of methylprednisolone, apparently at low ng/ml concentrations in urine, has been reported at 28 days after the last intra-articular administration of methylprednisolone, as set forth in the Brass Hat matter [23].

7.3.12 PHENYLBUTAZONE (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Phenylbutazone (Oxyphenylbutazone)**

Regulatory Limit: **5,000 ng/ml, from/in plasma/serum**

This 5,000 ng/ml threshold is well established in North America and was adopted by the RMTC/ARCI. Arizona, Arkansas, California, Colorado, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Montana, Nebraska, New Mexico, Ohio, Oklahoma, Oregon, Texas, Washington, Virginia, West Virginia, and Wyoming have adopted a threshold/regulatory limit of 5,000 ng/ml for phenylbutazone, an ARCI class 4 substance. Arkansas has adopted a threshold/regulatory limit of 3,000 ng/ml for phenylbutazone. The USEF has adopted a plasma/serum threshold/regulatory limit of 15,000 ng/ml phenylbutazone. Maryland, New Jersey, and Virginia have adopted a threshold/regulatory limit of 2,600 ng/ml for phenylbutazone in serum/plasma. Delaware has adopted a plasma threshold/regulatory limit of 2,500 ng/ml. Maryland and Pennsylvania have adopted a threshold/regulatory limit of 2,000 ng/ml for phenylbutazone. Idaho, Massachusetts, and Michigan recognize a urinary threshold/regulatory limit for phenylbutazone of 165 µg/ml. According to the *AAEP Guidelines for Drug Detection Times*, "a detection time of 48 hours is likely if phenylbutazone has been administered in a multiple dosing regimen and the threshold is 5 µg/ml. Single intravenous doses of 2 grams of phenylbutazone produce plasma concentrations that are below the 5 µg/ml threshold by 24 hours after the dose" [24]. No quantitative uncertainty estimates accompany these statements. The RMTC/ARCI and Louisiana have also adopted subthreshold levels for phenylbutazone of 1 µg/ml in plasma/serum.

AAEP-Standardized Therapeutic Dosage Regimen for Phenylbutazone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
1-2 GM	IV, PO	SID, BID	NSAID	24 HRS

TOBA Testing:

For phenylbutazone, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 2 µg/ml in plasma and the analyte detected is phenylbutazone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of phenylbutazone at any of the above thresholds/regulatory limits are available at this time. Deuterated phenylbutazone (D_9Phenylbutazone) for use as an internal standard in quantitative

analytical work has been made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

7.3.13 PREDNISOLONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Prednisolone**

Regulatory Limit: **1,000 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for prednisolone, an ARCI class 4 therapeutic medication and the principal active metabolite of prednisone. Prednisolone is, by law, a permitted race day medication in Florida.

AAEP-Standardized Therapeutic Dosage Regimen for Prednisolone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
200-500 MG	IV, IM	SID	STEROIDAL ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

For prednisolone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is prednisolone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of prednisolone at the above threshold/regulatory limit are available at this time.

7.3.14 PREDNISONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Prednisone**

Regulatory Limit: **100 ng/ml, from/in urine**

Ohio (1999) has adopted this threshold/regulatory limit for prednisone, an ARCI class 4 therapeutic medication, and this threshold/regulatory limit is also under review in at least one other state.

AAEP-Standardized Therapeutic Dosage Regimen for Prednisone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
200-400 MG	IM, PO	SID, BID	STEROIDAL ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

For prednisone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine.Tthe analyte detected is prednisone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of prednisone at the above threshold/regulatory limit are available at this time.

7.3.15 STANOZOLOL (Androgenic-Anabolic Steroid (AAS))

REGULATORY ANALYTE: **16β-hydroxystanozolol**

Threshold/Regulatory Limit: **1ng/ml, from/in urine**

Interim ARCI model rules communicated in April 2008 and based on urine testing recognize this threshold/regulatory limit for stanozolol (16β-hydroxystanozolol), an ARCI class 4 therapeutic medication, in all horses regardless of sex, apparently as total free and conjugated, recovered from urine.

NOTE: The presence of more than one of the four AAEP-/RMTC-/ARCI-approved anabolic steroids above, at concentrations greater than the individual thresholds indicated for each substance so identified, is not permitted.

AAEP-Standardized Therapeutic Dosage Regimen for Stanozolol:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
250-500 MG	IM	ONCE/1-3 WEEKS	ANABOLIC STEROID	48 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of stanozolol at the above threshold/regulatory limit is available at this time.

NOTE: At press time, there are suggestions that these AAS urinary regulatory thresholds are interim, and that a plasma threshold for stanozolol and associated scientifically determined withdrawal time guidelines will be developed by RMTC and presented for implementation on an accelerated basis.

On March 18, 2008, Pennsylvania announced a six-month interim plasma threshold for stanozolol to begin on April 1, 2008, as follows: 200-999 pg/ml, written reprimand

including concentration information. A test, equal to or greater than 1,000 pg/ml, constitutes an offense. For a horse that has received a reprimand, a second offense occurs when the horse subsequently tests at a concentration more than 10% above the "benchmark" test, i.e., the test that resulted in the reprimand.

7.3.16 Other Published Regulatory Thresholds for ARCI Class 4 Therapeutic Medications:

7.3.16.1 BENZOCAINE: (local anesthetic)

REGULATORY ANALYTE: **Benzocaine**

Threshold/Regulatory Limit: **50 ng/ml, from/in urine**

California, Washington, and New Mexico have adopted this threshold/regulatory limit for benzocaine, an ARCI class 4 therapeutic medication.

Standardized Therapeutic Dosage Regimen for Benzocaine:

No AAEP-standardized therapeutic dosage regimen is currently available for benzocaine.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of benzocaine at the above threshold/regulatory limit is available at this time.

7.3.16.2 ELTENAC (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Eltenac**

Threshold/Regulatory Limit: **100 ng/ml, from/in plasma/serum**

The USEF has adopted this threshold/regulatory limit for eltenac, an ARCI class 4 therapeutic medication.

Standardized Therapeutic Dosage Regimen for Eltenac:

No AAEP-standardized therapeutic dosage regimen is currently available for eltenac.

USEF-recommended maximum dosage per pound body weight for Eltenac is:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
0.25 MG/LB	IV			12 HRS

TOBA Testing:

For eltenac, the TOBA-suggested screening method is HPLC, and the suggested minimum concentration is 100 ng/ml in urine.The analyte detected is eltenac.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of eltenac at the above threshold/regulatory limit is available at this time.

7.3.16.3 FIROCOXIB (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Firocoxib**

Threshold/Regulatory Limit: **240 ng/ml, from/in plasma/serum**

The USEF has adopted this threshold/regulatory limit for firocoxib, an ARCI class 4 therapeutic medication.

Standardized Therapeutic Dosage Regimen for Firocoxib:

No AAEP-standardized therapeutic dosage regimen is currently available for firocoxib.

The USEF-recommended maximum dosage per pound of body weight for firocoxib is:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
0.0455 MG/LB 0.1 MG/LG	ORAL			12 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of firocoxib at the above threshold/regulatory limit are available at this time.

7.3.16.4 FLUMETHASONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Flumethasone**

Threshold/Regulatory Limit: **10 ng/ml, from/in urine**

Ohio (1999) adopted this threshold/regulatory limit for flumethasone, an ARCI class 4 therapeutic medication, and this threshold/regulatory limit is also under review in another state.

Standardized Therapeutic Dosage Regimen for Flumethasone:

No AAEP-standardized therapeutic dosage regimen is currently available for flumethasone.

TOBA Testing:

For flumethasone, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine.Tthe analyte detected is flumethasone.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of flumethasone at the above threshold/regulatory limit is available at this time.

7.3.16.5 IBUPROFEN (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Ibuprofen**

Threshold/Regulatory Limit: **100 ng/ml, from/in plasma/serum**

Kentucky has adopted this threshold/regulatory limit for ibuprofen, an ARCI class 4 therapeutic medication.

AAEP-Standardized Therapeutic Dosage Regimen for Ibuprofen:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
4-10 GMS	PO	BID	NSAID	24 HRS

TOBA Testing:

For ibuprofen, the TOBA-suggested screening method is HPLC, and the suggested minimum concentration is 100 ng/ml in urine. The analyte detected is ibuprofen.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of ibuprofen at the above threshold/regulatory limit is available at this time.

7.3.16.6 MECLOFENAMIC ACID (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Meclofenamic Acid**

Threshold/Regulatory Limit: **1,000 ng/ml, from/in plasma**

Ohio (1999), Idaho, Kentucky, and New Mexico have adopted this threshold/regulatory limit for meclofenamic acid, an ARCI class 4 therapeutic medication. The USEF has adopted a threshold/regulatory limit of 2,500 ng/ml meclofenamic acid in plasma/serum.

AAEP-Standardized Therapeutic Dosage Regimen for Meclofenamic Acid:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
500-1000 MG	PO	BID	NSAID	24 HRS

TOBA Testing:

For meclofenamic acid, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 100 ng/ml in urine. The analyte detected is meclofenamic acid.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of meclofenamic acid at the above threshold/regulatory limit are available at this time.

NOTE: Meclofenamic acid is an oral medication, the dose is large, the plasma half-life may be long, meclofenamic acid seems to be chemically stable in the environment, and testing can be highly sensitive; as such, traces of meclofenamic acid have been reported detected for long periods after the last nominal administration, most likely associated with an environmental presence and resulting in inadvertent re-exposure.

7.3.16.7 NAPROXEN (non-steroidal anti-inflammatory)

REGULATORY ANALYTE: **Naproxen**

Regulatory Limit: **5,000 ng/ml, from/in plasma/serum**

Idaho has adopted this threshold/regulatory limit for naproxen, an ARCI class 4 therapeutic medication, and this threshold/regulatory limit is also under review in at least one other state. This threshold/regulatory limit is supported by Canadian research. Oklahoma has adopted a threshold/regulatory limit of 750 ng/ml for naproxen in plasma, and the USEF has adopted a threshold/regulatory limit of 40,000 ng/ml for naproxen. Oklahoma has published a urinary threshold of 165 µg/ml for naproxen. Louisiana recognized a 750 ng/ml plasma/serum threshold for naproxen as of August 2007 but has since adopted a zero tolerance policy for this medication. Review of an 05 unpublished RMTC document suggests that Ohio may have a 10,000 ng/ml threshold in plasma.

AAEP-Standardized Therapeutic Dosage Regimen for Naproxen:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
4-5 GM	PO	SID, BID	NSAID	24 HRS

TOBA Testing:

For naproxen, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 100 ng/ml in urine and the analyte detected is naproxen.

Withdrawal Time Guideline:

To our knowledge, no withdrawal time guidelines linked to a standardized therapeutic dosage of naproxen at the above threshold/regulatory limit are available at this time.

NOTE: Naproxen is an oral medication, the dose is large, and naproxen seems to be chemically stable in the environment, and testing can be highly sensitive; as such, traces of naproxen have been reported detected for long periods after the last nominal administration, most likely associated with its environmental presence and resulting in inadvertent re-exposure.

7.3.16.8 Nine other AAEP/RMTC/ARCI recognized class 4 therapeutic medications, namely aminocaproic acid, beclomethasone, guaifenesin (expectorant/muscle relaxant), fluoroprednisolone, methylergonovine, pentoxyfylline, phenytoin (muscle relaxant), triamcinolone (steroidal anti-inflammatory), and trichlormethiazide (diuretic), are recognized therapeutic medications (see Appendix III) for which no scientifically determined and published thresholds/regulatory limits or withdrawal time guidelines are currently available. Deuterated guaifenesin for use as a stable isotope internal standard in quantitative analytical work has been synthesized and made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

7.3.16.8.1: AMINOCAPROIC ACID (Prophylaxis of EIPH)

REGULATORY ANALYTE: **aminocaproic acid**

Aminocaproic acid (as Amicar ®) may be administered on race day for the prevention or alleviation (prophylaxis) of EIPH. Some states permit administration of Amicar up to two hours prior to post.

AAEP-/ RMTC-Standardized Therapeutic Dosage Regimen for Amicar:

The following is the standardized therapeutic dosage for Amicar of the RMTC advisory committee.

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2.5 - 5 g	IV	SID	Adjunct Bleeder	24 HRS

TOBA Testing:

No suggested testing recommendations.

Withdrawal Time Guideline:

Administration is generally not permitted closer than two to three hours to post.

NOTE: On January 1, 2008, the Pennsylvania State Horse Racing Commission banned the use of Amicar due to lack of scientific evidence as to the efficacy of the drug in the prophylaxis of EIPH.

7.3.16.8.2: BECLOMETHASONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: none identified

No available Threshold/Regulatory Limit:

AAEP-Standardized Therapeutic Dosage Regimen for beclomethasone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
3 - 6 PUFFS	INHALER (MDI)	ONCE	STEROIDAL ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

No suggested testing recommendations.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of beclomethasone is available at this time.

7.3.16.8.3: GUAFENESIN (expectorant/muscle relaxant**)**

REGULATORY ANALYTE: guafenesin

No available Threshold/Regulatory Limit:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
DOSAGE VARIABLE (ORAL PREPS)	PO	SID/BID	EXPECTORANT	48 HRS

AAEP-Standardized Therapeutic Dosage Regimen for guafenesin:

TOBA Testing:

For guafenesin, the TOBA-suggested screening methods is TLC and HPLC, and the suggested minimum limit of detection is 100 nanograms per milliliter in urine and the analyte detected is guanefenesin.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of guafenesin is available at this time.

Deuterated guaifenesin (D_4Guaifenesin) for use as a stable isotope internal standard in quantitative analytical work has been synthesized and made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

7.3.16.8.4: FLUOROPREDNISOLONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: fluoroprednisolone

No available threshold/regulatory limit:

AAEP-Standardized Therapeutic Dosage Regimen for fluoroprednisolone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-20 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	48 HRS

TOBA Testing:

No criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of fluoroprednisolone is available at this time.

7.3.16.8.5: METHYLERGONOVINE (EIPH)

REGULATORY ANALYTE: undefined

No available thresholdregulatory limit:

AAEP-Standardized Therapeutic Dosage Regimen for methylergonovine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
5-10 MG	IV, IM	SID	EIPH	24 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of methylergonovine are available at this time.

7.3.16.8.5: PENTOXIFYLLINE (steroidal anti-inflammatory)

REGULATORY ANALYTE: pentoxifylline

No available treshold/regulatory limit:

AAEP-Standardized Therapeutic Dosage Regimen for pentoxifylline:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-4 GM	PO	BID	PERIPHERAL VASOLDILATOR	48 HRS

TOBA Testing:

For pentoxifylline, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum limit of detection is 20 ng/ml in urine and the analyte detected is pentoxifylline.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of pentoxifylline is available at this time.

7.3.16.8.6: PHENYTOIN (exertional myositis),

REGULATORY ANALYTE: phenytoin

No available threshold/regulatory limit:

AAEP-Standardized Therapeutic Dosage Regimen for phenytoin:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
3-5 GM	PO	SID	EXERTIONAL MYOSITIS	48 HRS

TOBA Testing: a

For phenytoin,the TOBA-suggested screening method is ELISA, and the suggested minimum limit of detection is 20 ng/ml in urine and the analyte detected is phenytoin and 5-hydroxyphenytoin

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of phenytoin is available at this time.

7.3.16.8.7: TRIAMCINOLONE (steroidal anti-inflammatory),

REGULATORY ANALYTE: triamcinolone

No available Threshold/Regulatory Limit:

AAEP-Standardized Therapeutic Dosage Regimen for triamcinolone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
2-18 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of triamcinolone is available at this time.

7.3.16.8.8: TRICHLORMETHIAZIDE: (diuretic),

REGULATORY ANALYTE: trichlormethiazide
No available threshold/regulatory limit:

AAEP-Standardized Therapeutic Dosage Regimen for trichlormethiazide:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
200-400 MG	PO	SID	DIURETIC (COMBINED W/ DEXAMTHASONE AS NAQUSONE)	24 HRS

TOBA Testing:
For trichlormethiazide:, the TOBA-suggested screening methods are TLC and HPLC, and the suggested minimum concentration is 100 ng/ml in urine and the analyte detected is trichlormethiazide.

Withdrawal Time Guideline:
To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of trichlormethiazide are available at this time.

NOTE: Buscopan and carbazochrome are two other RMTC/ARCI-recognized therapeutic medications that are currently unclassified under the ARCI Uniform Classification Guidelines for Foreign Substance. No scientifically determined and published thresholds/regulatory limits or withdrawal time guidelines are currently available for either buscopan or carbazochrome, although carbazochrome is listed as RMTC "research already under way" (Appendix III-A).

7.4 ARCI Class 5 Therapeutic Medications

7.4.1 DIMETHYLSULFOXIDE (non-steroidal anti-inflammatory)
REGULATORY ANALYTE: **Dimethylsulfoxide (DMSO)**

Regulatory Limit: **10,000 ng/ml, from/in serum/plasma**
Oregon and Kentucky have adopted this threshold/regulatory limit for DMSO, an ARCI class 5 therapeutic medication. Oklahoma has adopted a threshold/regulatory limit of 1 µg/ml serum, and Illinois has adopted a threshold/regulatory limit of 500 µg/ml in urine.

Standardized Therapeutic Dosage Regimen for dimethylsulfoxide:
No AAEP-standardized therapeutic dosage regimen is currently available for dimethyl sulfoxide.

In an unpublished document, the RMTC Advisory Committee recommends the following dosage regimen for DMSO:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT-OFF
1 MG/KG	IV or PO	SID	ANTI-INFLAMMATORY	24 HRS

TOBA Testing:

No suggested criteria

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of DMSO at the above threshold/regulatory limits are available at this time.

NOTE: Dimethylsulfoxide is a naturally occurring environmental substance, found in rainwater, and it is also identifiable in all horses, presumably as a result of intestinal fermentation, so it is also endogenous in the horse. However, as the only ARCI class 5 substance with a regulatory threshold, and considering the very high concentration of the regulatory threshold, we have elected to present it as an ARCI class 5 therapeutic medication.

7.5 Other Published Regulatory Thresholds for Therapeutic Medications

7.5.1 SULFA DRUGS (antimicrobial)

REGULATORY ANALYTE: **Parent substance**

Regulatory Limit: **1,000 ng/ml, from/in urine**

Oregon has adopted this threshold/regulatory limit for sulfonamide containing therapeutics.

Standardized Therapeutic Dosage Regimen for Sulfa Drugs:

No AAEP-standardized therapeutic dosage regimen is currently available for sulfa drugs.

TOBA Testing:

No suggested criteria

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of sulfonamide medications at the above threshold/regulatory limits are available at this time.

NOTE: Most U.S. and international regulatory authorities do not regulate the use of sulfonamide or other antibiotic medications. In this regard, the ARCI Uniform Classification Guideline for Foreign Substances does *not* include antimicrobials, antiparasitic drugs, and nutrient substances such as vitamins. Listed examples of antibiotics include sulfonamides and trimethoprim, penicillins, cephalosporins, chloramphenicol, aminoglycosides, tetracyclines, nitrofurans, and metronidazole. Listed anthelmintics include avermectins, benzimidazoles, piperazines, pyrantel, and tetramizole. Listed vitamins include vitamins A, D, E, K, and B vitamins and vitamin C.

8. Furosemide and Other Agents Used to Prevent and/or Treat Exercise-Induced Pulmonary Hemorrhage (EIPH)

Medications to reduce the incidence of exercise-induced pulmonary hemorrhage (EIPH) include furosemide (Salix®), aminocaproic acid (Amicar®), carbazochrome, Premarin, and tranexamic acid. No EIPH-related medication should be administered closer than three hours prior to post.

8.1 FUROSEMIDE (Prophylaxis of EIPH)

REGULATORY ANALYTE: **furosemide**
Regulatory Limit: **100 ng/ml, from/in plasma (if urinary specific gravity <1.010)**

Furosemide (as Salix) may be administered on race day for the prevention or alleviation (prophylaxis) of EIPH. A number of states permit administration of furosemide up to three hours prior to post. The recommended dose of furosemide varies from 150 to 500 mg by single intravenous injection. Optimal regulatory control of the use of furosemide is by quantification of urinary specific gravity and serum furosemide concentrations. A violation of the furosemide rule may be deemed to have occurred if the urinary specific gravity is less than 1.010 and the serum concentration of furosemide is greater than 100 ng/ml.

AAEP-Standardized Therapeutic Dosage Regimen for Furosemide:

No AAEP-standardized therapeutic dosage regimen is currently available for furosemide; the ARCI model rule for furosemide suggests a dose of not less than 150 mg and not greater than 500 mg, by single intravenous injection, with administration no less than four hours prior to post.

TOBA Testing:

For furosemide, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 50 ng/ml in plasma. The analyte detected is furosemide.

Withdrawal Time Guideline:

The serum regulatory threshold and the scientifically linked four-hour withdrawal time guideline are based on HBPA-supported research, and deuterated furosemide for use as an internal standard in association with quantitative analytical work has been made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, Appendix IV]

NOTE: Particular care should be taken to ensure that regulatory samples are drawn from the opposite vein/side from which Salix was administered (see Appendix I, Section 7.2).

8.2 Other Adjunct Medication for EIPH

The use of certain approved adjunct bleeder and other adjunct medications in combination with Salix may be permitted, with appropriate information communicated to the betting public. The use of adjunct prophylactic medications such as aminocaproic acid (Amicar), carbazochrome, Premarin, and tranexamic acid may be permitted at the discretion of the treating veterinarian, as is the practice in a number of jurisdictions as is set forth below for the state of Virginia.

Virginia Permissible Adjunct Bleeder Medications

Medication	Maximum Permitted Dosage
Conjugated estrogens	25 mg
Aminocaproic acid	2.5 g
Tranexamic acid	1 g
Carbazochrome	5 ml

9. Endogenous, Dietary, and Environmental Substances

For the purposes of this document, endogenous, dietary, and environmental substances are ARCI-classified substances that are produced by horses or that unavoidably become part of the food supply or environment of the horse.This class of substances is explicitly recognized by the RMTC/ARCI. Endogenous, dietary, and/or environmental substances that are also ARCI-classified substances include atropine, benzoylecgonine, boldenone, bufotenine, caffeine, dimethylsulfoxide (DMSO), hydrocortisone, morphine glucuronides, nandrolone, salicylic acid/salicylates, testosterone, and theobromine. Three of these endogenous substances, boldenone, nandrolone, and testosterone, are also RMTC/ARCI therapeutic medications, and one,

atropine, is a dietary substance. A number of states have established thresholds/regulatory limits for these endogenous, dietary, and environmental substances, as follows:

9.1 ATROPINE (anti-cholinergic)

REGULATORY ANALYTE: **Atropine**
Threshold/Regulatory Limit: **10 ng/ml from/in urine**

California and New Mexico have adopted this threshold/regulatory limit for atropine, an ARCI class 3 substance. Two other jurisdictions, Oklahoma and Louisiana, have adopted thresholds of 70 ng/ml and 75 ng/ml in urine, respectively.

AAEP-Standardized Therapeutic Dosage Regimen of Atropine:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
9 MG OPHTHALMIC OINTMENT	INTRA-SYNOVIAL TOPICAL	ONCE SID	CHRONIC SYNOVITIS MYDRAISIS	48 HRS

TOBA Testing:

For atropine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is atropine.

Withdrawal Time Guideline:

While atropine is a dietary/environmental substance, it is also an AAEP/RMTC/ARCI therapeutic medication; however, to our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of atropine at the above threshold/regulatory limit are available at this time.

9.2 BENZOYLECGONINE

REGULATORY ANALYTE: **Benzoylecgonine**
Threshold/Regulatory Limit: **150 ng/ml, in urine**

Illinois, Louisiana, Ohio, and Oklahoma have adopted this threshold/regulatory limit for benzoylecgonine, the major urinary metabolite of an ARCI class 1 substance and an environmental substance. This threshold/regulatory limit is also in place in several other jurisdictions. In Florida, the Division of Pari-Mutuel Wagering and the Florida Horsemen's Benevolent and Protective Association have agreed upon an unpublished "in-house" threshold/regulatory limit of 100 ng/ml benzoylecgonine in urine. Washington has adopted a threshold/regulatory limit of 50 ng/ml benzoylecgonine in urine. [26, 27] Louisiana has also adopted a plasma/serum threshold for benzoylecgonine of < 1 ng/ml.

TOBA Testing:

For benzoylecgonine (cocaine), the TOBAsuggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is benzoylecgonine.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.3 BOLDENONE (Androgenic-Anabolic Steroid (AAS))

REGULATORY ANALYTE: **Boldenone**

Threshold/Regulatory Limit: **15 ng/ml, from/in urine in intact males. No level is permitted in geldings, fillies, or mares.**

Interim ARCI model rules communicated in April 2008 and based on urine testing recognize this threshold/regulatory limit for boldenone, an ARCI class 4 therapeutic medication, in male horses other than geldings, apparently as total free and conjugated boldenone recovered from urine.

TOBA Testing:

No suggested criteria.

NOTE: The presence of more than one of the four AAEP-/RMTC-/ARCI-approved androgenic anabolic steroids above, at concentrations greater than the individual thresholds indicated for each substance so identified, is not permitted.

AAEP-Standardized Therapeutic Dosage Regimen for Boldenone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
125-500 MG	IM	ONCE/2-3 WEEKS	ANABOLIC	48 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of boldenone at the above threshold/regulatory limit are available at this time.

NOTE: At press time, there are suggestions that these AAS urinary regulatory thresholds are interim, and that a plasma threshold for boldenone and associated withdrawal time

guidelines will be developed by the RMTC and presented for implementation on an accelerated basis.

On March 18, 2008, Pennsylvania announced a six-month, interim plasma threshold for boldenone starting on April 1, 2008, as follows: 200-999 pg/ml, written reprimand **including concentration information. A test, equal to or greater than 1,000 pg/ml, constitutes an offense. For a horse that has received a reprimand, a second offense occurs when the horse subsequently tests at a concentration more than 10% above the "benchmark" test, i.e., the test that resulted in the reprimand.**

9.4 BUFOTENINE

REGULATORY ANALYTE: **Bufotenine**
Threshold/Regulatory Limit: Listed as Non-Classified

The ARCI lists bufotenine as a non-classified substance, notes that is not available commercially in any form, and that *it may be found in horse urine* as a metabolite of 3-methyl-N-N dimethyltryptamine, found in reed canary grass and potentially in other food source plants. As such, bufotenine has been found in the urine of horses eating this grass, and possibly other grasses, and has been reported as a "positive" finding. The ARCI document further notes (page 34) that "findings of bufotenine in equine urine should not be considered for regulatory action."

NOTE: Bufotenine is unusual in that it is regulated as a schedule 1 drug by the U.S. Drug Enforcement Agency (DEA) and is classified as a Schedule 1 controlled substance according to the criminal code regulations of Australia.

TOBA Testing:
No suggested criteria.

Withdrawal Time Guideline:
No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.5 CAFFEINE

REGULATORY ANALYTE: **Caffeine**
Threshold/Regulatory Limit: **100 ng/ml from/in serum/plasma**
RMTC/ARCI model rule recognizes 100 ng/ml in plasma as a national regulatory threshold for caffeine, and other jurisdictions have broadly similar thresholds. Maryland, Nebraska, Ohio, Oregon, and Washington have adopted this threshold/regulatory limit for caffeine, an ARCI class 2 substance and a common environmental substance. This threshold/regulatory limit is well supported by published research [28, 29], and it or related thresholds/regulatory limits are also in place in several other jurisdictions.

Louisiana has adopted a plasma/serum threshold/regulatory limit for caffeine of 25 ng/ml. Two commissions, namely Louisiana and Oklahoma, have adopted a urinary threshold/regulatory limit for caffeine of 100 ng/ml [29], and Florida has adopted a urinary threshold/regulatory limit of 200 ng/ml. Canada appears to recognize long-established thresholds for caffeine of 250 ng/ml in plasma and 1,000 ng/ml in urine.

TOBA Testing:

For caffeine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 100 ng/ml in plasma. The analyte detected is caffeine.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.6 HYDROCORTISONE (steroidal anti-inflammatory)

REGULATORY ANALYTE: **Hydrocortisone**

Threshold/Regulatory Limit: **1,000 ng/ml, from/in urine**

Ohio (1999) adopted this Australian/international threshold/regulatory limit for hydrocortisone, an ARCI class 4 therapeutic medication.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

While this is an endogenous substance, it is also used as a therapeutic medication; however, to our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of hydrocortisone at the above threshold/regulatory limit are available at this time.

9.7 MORPHINE GLUCURONIDES

REGULATORY ANALYTE: **Morphine**

Threshold/Regulatory Limit: **100 ng/ml, in urine**

In the United States, a number of thresholds/regulatory limits are currently in place for morphine glucuronides, the major urinary metabolites of an ARCI class 1 substance, a not uncommon addition to human foodstuffs as poppy seeds and also a potential environmental substance. The threshold/regulatory limit in Louisiana is 120 ng/ml [2;, in Oklahoma, it is 100 ng/ml; a slightly lower (50 ng/ml) limit is in place in Ohio (1999) and Washington, and also, more recently, in the United Kingdom. This threshold/regulatory limit is also under review in more than one jurisdiction. These thresholds/regulatory limits are supported by research from the Horseracing Forensic Laboratory (HFL) in England [31], which shows urinary concentrations of 110 ng/ml after administration to horses of 2-gram doses of poppy seeds containing 3 μg of morphine per dose [30, 31, 32]. These thresholds/regulatory limits are dramatically lower than the 2,000-ng/ml "cut-off" in place

in human workplace medication testing [33, 34], and morphine glucuronide thresholds/regulatory limits are in place in several other jurisdictions [32]. Louisiana also recognizes a serum/plasma threshold for morphine of < 1 ng/ml.

TOBA Testing:

For morphine, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine.Tthe analyte detected is morphine.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.8 NANDROLONE (Androgenic-Anabolic steroid (AAS))

REGULATORY ANALYTE: **5α-oestrane-3β,17α-diol**

Threshold/Regulatory Limit: **1 ng/ml, from/in urine in geldings, fillies and mares**
45 ng/ml, from/in urine in intact males

5α-oestrane-3β,17α-diol, Oestranediol, EAD, is a major urinary metabolite fragment of nandrolone. Interim ARCI model rules communicated in April 2008 and based on urine testing recognize a 1 ng/ml threshold/regulatory limit for nandrolone, an ARCI class 4 therapeutic medication, in geldings, fillies, and mares and 45 ng/ml in intact males.

NOTE: The presence of more than one of the four AAEP-/RMTC-/ARCI-approved androgenic anabolic steroids above, at concentrations greater than the individual thresholds indicated for each substance so identified, is not permitted.

AAEP-Standardized Therapeutic Dosage Regimen for Nandrolone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
100-200 MG	IM	ONCE/1-2 WEEKS	ANABOLIC STEROID	48 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guideline linked to a standardized therapeutic dosage of nandrolone at the above threshold/regulatory limit are available at this time.

NOTE: At press time, there are suggestions that these AAS urinary regulatory thresholds are interim, and that a plasma threshold for nandrolone and associated withdrawal time

guidelines will be developed by the RMTC and presented for implementation on an accelerated basis.

On March 18, 2008, Pennsylvania announced a six-month interim plasma threshold for nandrolone starting April 1, 2008, as follows: 200-999 pg/ml, written reprimand **including concentration information. A test, equal to or greater than 1,000 pg/ml, constitutes an offense. For a horse that has received a reprimand, a second offense occurs when the horse subsequently tests at a concentration more than 10% above the "benchmark" test; i.e., the test that resulted in the reprimand.**

9.9 SALICYLIC ACID/SALICYLATES

REGULATORY ANALYTE: **Salicylic Acid**
Threshold/Regulatory Limit: **750,000 ng/ml, from/in urine**

Ohio (1999), Texas, California, Washington and New Mexico have adopted this threshold/regulatory limit for salicylic acid, an ARCI class 4 substance. This is also the generally accepted international threshold/regulatory limit for salicylates. Oklahoma has adopted a serum/plasma threshold/regulatory limit for salicylates of 65,000 ng/ml.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.10 SCOPOLAMINE

REGULATORY ANALYTE: **Scopolamine**
Threshold/Regulatory Limit: **75 ng/ml, from/in urine**

Louisiana has adopted this threshold/regulatory limit for scopolamine, an ARCI class 3 substance.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.11 STRYCHNINE

REGULATORY ANALYTE: **Strychnine**
Threshold/Regulatory Limit: **100 ng/ml, from/in urine**

Oklahoma and Louisiana have adopted this threshold/regulatory limit for strychnine, an ARCI class 1 substance.

TOBA Testing:

For strychnine, the TOBA-suggested screening methods are TLC and GC/MS, and the suggested minimum concentration is 20 ng/ml in urine and the analyte detected is strychnine.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.12 TESTOSTERONE (Androgenic-Anabolic steroid)

REGULATORY ANALYTE: **Testosterone**

Threshold/Regulatory Limit: **20 ng/ml, from/in urine in geldings and 55 ng/ml in fillies and mares**

Interim ARCI model rules communicated in April 2008 and based on urine testing recognize this threshold/regulatory limit for testosterone, an ARCI class 4 therapeutic medication. Intact male horses will not be tested.

NOTE: The presence of more than one of the four AAEP-/RMTC-/ARCI-approved androgenic anabolic steroids above, at concentrations greater than the individual thresholds indicated for each substance so identified, is not permitted.

AAEP-Standardized Therapeutic Dosage Regimen for Testosterone:

DOSAGE	ROUTE	FREQUENCY	CLINICAL USE	CLINICAL CUT OFF
500-1000 MG	IM	ONCE/1-3 WEEKS	ANABOLIC STEROID	48 HRS

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

To our knowledge, no scientifically determined and published withdrawal time guidelines linked to a standardized therapeutic dosage of testosterone at the above threshold/regulatory limit are available at this time.

NOTE: At press time, there are suggestions that these AAS urinary regulatory thresholds are interim and that a plasma threshold for testosterone and associated withdrawal time guidelines will be developed by the RMTC and presented for implementation on an accelerated basis.

On March 18, 2008, Pennsylvania announced a six-month interim plasma threshold for testosterone in intact males starting April 1, 2008, as follows: 1,000–1,999 pg/ml, written reprimand **including concentration information. A test, equal to or greater than 2000 pg/ml, constitutes an offense. For a horse that has received a reprimand, a second offense occurs when the horse subsequently tests at a concentration more than 10% above the "benchmark" test, i.e., the test that resulted in the reprimand.**

9.13 THEOBROMINE

REGULATORY ANALYTE: **Theobromine**
Threshold/Regulatory Limit: **2,000 ng/ml, from/in urine**

Ohio (1999), Texas, and Washington have adopted this long-established international threshold/regulatory limit for theobromine, an ARCI class 4 substance. This is also the generally accepted international threshold/regulatory limit for theobromine. Florida has adopted a threshold/regulatory limit of 400 ng/ml in urine for theobromine.

NOTE: The original work in the early 1980s on which this regulatory threshold was based involved a very small number (three) of horses. More recent work by Sams and colleagues [35] has shown that daily oral dosing with relatively small numbers of chocolate-covered peanuts can result in urinary concentrations of theobromine in the order of 12,000 ng/ml. In this regard, the International Equestrian Federation (FEI) recently (2006) took caffeine off its "must pursue" list.

TOBA Testing:

No suggested criteria.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

9.14 THEOPHYLLINE

REGULATORY ANALYTE: **Theophylline**
Threshold/Regulatory Limit: **400 ng/ml, from/in urine**

Florida has adopted this threshold/regulatory limit for theophylline, an ARCI class 3 substance.

TOBA Testing:

For theophylline, the TOBA-suggested screening method is ELISA, and the suggested minimum concentration is 20 ng/ml in urine. The analyte detected is theophylline.

Withdrawal Time Guideline:

No withdrawal time guidelines, since these are neither relevant nor applicable to endogenous, dietary, and environmental substances.

10. Testing Laboratories, Administrative Procedures, and Analytical Findings

10.1 The NHBPA policy on testing laboratories[16] is consistent with those of ARCI in that all testing laboratories shall be accredited to American Association for Laboratory Accreditation (A2LA) standards, or International Standards Organization (ISO)/International Electrotechnical Commission (IEC) 17025 standards, or their equivalent, as set forth in Appendix VI.

10.2 All administrative procedures associated with medication violations shall remain confidential until completion of the entire administrative process.

10.3 These administrative procedures shall include a split sample rule following the principles set forth in the ARCI Model Rules. [36]

10.4 For all analytical findings for regulatory analytes with thresholds/regulatory limits, the regulatory process shall include determination of the concentration of analytes in the test sample by a validated, peer-reviewed method[17] or, failing that, the best available method.

10.5 If the primary laboratory reports the presence of a foreign substance/regulatory analyte at a concentration greater than the threshold/regulatory limit, then the trainer or the trainer's designated representative shall have the opportunity to **designate any laboratory accredited to A2LA or ISO/IEC 17025 standards** as set forth in 10.1 above as his or her "split sample" or "reference" laboratory to obtain a quantitative[18] determination of the analyte. He/she shall also be **free to request any additional testing of the sample whatsoever,** including genetic testing, as may be required to assist in his or her defense and/or the authorities in their review of the circumstances giving rise to the chemical identification in question.

10.6 All quantitative results/reports shall include a statistical estimate of the **measurement of uncertainty**[19]. No regulatory analyte shall be reported as "positive" unless the lower limit of the 95% **confidence limit**[20] for the measured concentration of the regulatory analyte is greater than the threshold/regulatory limit.

11. Expert Professional Review

11.1 The NHBPA hereby endorses and supports the 1995 recommendation of the ARCI that "all chemical findings in official test samples be subjected to a documented review process by a veterinary pharmacologist prior to any regulatory action." [5]

11.2 The NHBPA endorses the use of an independent Equine Medical Director (EMD), as set forth by the California Horse Racing Board. The EMD should oversee implementation of the guidelines established above and promote research aimed at identifying thresholds/regulatory limits for therapeutic medications and endogenous, dietary, and environmental substances. The EMD should also contribute to the development of

withdrawal time guidelines for therapeutic medications and educate the racing community at large on matters affecting preservation of the health and welfare of racing horses.

12. Further Research

12.1 Blood Testing

The NHBPA recognizes that blood, as a regulatory sample, yields data that are, in forensic terms, much more confidently interpretable than urinary data. The NHBPA also notes that recent advances in analytical chemistry, and specifically LC-MS and LC-MS-MS technology, increasingly make possible the quantitative confirmation of therapeutic medications in blood plasma and serum samples, as has been demonstrated for clenbuterol [13] and as is part of the RMTC mission.

The NHBPA therefore recommends that all testing laboratories have in place LC-MS or LC-MS-MS testing technology to optimize regulatory practices for horse racing and to better preserve the health and welfare of horses.

Application of LC-MS and LC-MS-MS testing technology will allow racing chemists to confirm and quantify an increasing number of ARCI class 2, 3, 4, and 5 therapeutic medications and endogenous, dietary, and environmental substances in blood, thereby avoiding many of the problems associated with urine testing. [5]

Compared with plasma testing, urine testing almost invariably does not allow as confident an interpretation of the pharmacological significance of quantitative data from urine because of the very large inherent variability in urinary concentrations of therapeutic medications and/or their metabolites (see Appendix I, Section 4).

Quantitative blood data can be more confidently interpreted than urinary data. The advantage for horses, horsemen, and the industry at large is that urinary findings may be found to be without regulatory significance based on negative or subthreshold quantitative data from the corresponding blood sample, a very significant regulatory advance. [13]

A further problem with urine testing has been that the analytes detected in urine are often unique metabolites or portions of metabolites of the medication in question. Analytical standards of these metabolites or metabolite portions/regulatory analytes can be unobtainable, difficult to obtain, of uncertain chemical stability, and challenging to accurately quantify in urine, all of which lead to significant technical problems and difficulties with quantitative urine testing. [6, 8, Appendices IV and V].

On the other hand, the analyte detected in a blood test is almost always the parent medication. Advantages of this technique are that suitable standards are virtually always available, these standards are generally stable, and it is almost always easier to accurately recover and quantify parent medications in blood than the more complex and poorly characterized metabolites or metabolite fragments/regulatory analytes of unknown

stability recovered from urine. This is a problem that has been specifically addressed by research supported by the National and local HBPAs (see Appendix V). In this regard, HBPA-supported research is currently directed toward making stable isotope reference standards for plasma and urinary quantitation of equine therapeutic medications/metabolites/metabolite fragments available to the racing industry and racing chemists worldwide. [6, 8, Appendices IV and V].

Additionally, to our knowledge, Salix® administration does not interfere with the detection or quantification of any medication in blood plasma or serum, again leading to more equitable regulation of therapeutic medication.

A further problem with urine testing is that some substances may be slow to accumulate in urine and may thus be non-detectable shortly after their administration. This deficit in urine testing could be exploited through the administration of performance-altering substances close to post. Blood testing suffers from no such limitations and can be a very reliable method of detecting the administration of performance-altering substances close to post. [13]

In summary, because it avoids the many technical and interpretational problems associated with urine testing, blood- or serum-based testing provides a significantly superior scientific basis for the regulation of therapeutic medication. As such, blood-based testing has the potential to significantly benefit horses, horsemen, and the industry at large.

On this basis, the NHBPA recommends and strongly supports the accelerated implementation of LC-MS or LC-MS-MS blood testing technology for therapeutic medications, with the goal of avoiding the many regulatory uncertainties inherent in urine testing.

12.2 Withdrawal Time Guidelines

As set forth in this Proposed National Policy on Drug Testing and Therapeutic Medication Regulation, thresholds/regulatory limits are a critical, indeed indispensable, regulatory tool; thresholds/regulatory limits expressed as regulatory analyte concentrations in plasma or urine, however, are not practically usable by most industry professionals. What industry professionals, and especially veterinarians and trainers, need are scientifically determined and published withdrawal time guidelines scientifically linked to the specific thresholds/regulatory limits in place in the jurisdiction.

A withdrawal time guideline is a *suggested* period before an event during which administration of a medication should cease in order to minimize the probability of exceeding the threshold/regulatory limit for the substance.

All withdrawal time guidelines are "best estimates." Adherence to a withdrawal time guideline merely serves to reduce the risk of inadvertently exceeding the

threshold/regulatory limit; *it can never guarantee that exceeding the threshold/regulatory limit will not occur*.

A more detailed definition of withdrawal time guidelines and their limitations is set forth under Appendix II: Definitions. A listing of "Factors Affecting Withdrawal Times" is set forth in Appendix I.

To our knowledge, the only scientifically determined and published withdrawal time guideline scientifically linked to a specific regulatory limit currently in place is that for furosemide. The original work on 49 horses was supported by the Kentucky HBPA, published in the refereed scientific literature [37] and forms the basis of the current RMTC/ARCI furosemide threshold/rule, and publication of the database makes it possible to estimate the uncertainty associated with this threshold. More recent, to date unpublished research, under the aegis of the California Horse Racing Board, has established the CHRB 50 ng/ml plasma threshold for flunixin, stated to be consistent with a 24-hour withdrawal time. Earlier unpublished research under the aegis of the California Horse Racing Board established the CHRB 25 pg/ml plasma threshold for clenbuterol, again stated to be consistent with a 96-hour withdrawal time.

In summary, the development of scientifically determined and **published withdrawal time guidelines linked** to each specific threshold/regulatory limit and the appropriate standardized dosage regimen for each therapeutic medication and with a statistically determined estimate of the uncertainty involved is a high research priority for most equine therapeutic medications, and this position is clearly set forth in Appendix III-A, "RMTC Therapeutic Medications Routinely Used and Identified as Necessary by the Veterinary Advisory Committee."

12.3 The NHBPA recognizes that the specifics of forensic testing and therapeutic medication and the sensitivity and scope of analytical methods change with time. Nothing in this policy shall be interpreted to preclude its modification in the light of increasing knowledge about the detection, actions, effects, and uses of performance-altering substances and the capability of identifying therapeutic medications or endogenous, dietary, or environmental substances in horses in training or racing.

Appendix I

Factors Affecting Withdrawal Times

It is important to allow an adequate withdrawal time between the last administration of a therapeutic medication and competition. Withdrawal times, however, are affected by a large number of poorly characterized or understood factors. Any guideline, therefore, is unlikely to be inclusive of all the possible variations that can affect the withdrawal time in any individual horse.

The following, in approximate order of their importance, is a list of factors that influence withdrawal times.

1. Dose

Medications administered at gram doses (2 to 10 g/horse), and especially if the dosing is repeated, are much more likely to be readily detectable and to be detectable for longer periods than medications administered as single doses at low milligram amounts (5 mg or less/horse).

Precaution:

Be aware of the actual quantity, in grams, milligrams, or micrograms per administration, of the medications you administer. Additionally, substances administered orally and at times even intravenously at gram/day doses may be retained in the dosing environment of the horse, resulting in apparently prolonged "detection times" for the medication. On the other hand, if a new horse is introduced into the medication administration environment, the conversion of such a previously negative horse to a trace level "positive" may occur, as has been reported for a number of therapeutic medications, as detailed in the Mistegic matter. [22] In circumstances where a horse is retained in or introduced to a stall that contains traces of a medication, what is being measured is not the rate at which the horse eliminates the medication *but rather the rate at which the medication is eliminated/eliminates from the stall in question.*

2. Sensitivity of the Testing Process

Increasing the sensitivity of a test by 100-fold or more is likely to greatly extend (perhaps triple) the withdrawal time.

Precaution:

If an ELISA test or, more recently, a highly sensitive LC-MS-MS method for an agent has been developed/introduced, a general rule is to at least double the withdrawal time that was used prior to development/introduction of the ELISA test. Additionally, LC-MS-MS technology is highly sensitive and can readily yield forensically irrelevant trace level identifications for many therapeutic medications, and this is apparently especially true in the case of urine testing for non-steroidal anti-inflammatory medications.

3. Local Testing Procedures

It is obvious from this document that testing methods/regulatory procedures are far from standardized, so what constitutes a violation ("positive ") in one jurisdiction may not necessarily constitute a violation ("positive") in another jurisdiction. For example, Canada has

limited sensitivity testing for therapeutic medications, and as a general rule Canadian "detection times"[21] are likely to be shorter than the "detection times" for the same medications in the United States.

Precaution:

Because the Canadian authorities have limited the sensitivity of their tests for many medications, all Canadian detection times should be treated with caution outside Canada.

NOTE*:*

The setting of a threshold/regulatory limit immediately standardizes testing for that medication in all jurisdictions adhering to that threshold/regulatory limit. Setting a threshold/regulatory limit immediately requires the laboratory to put into place specific analytical procedures that allow it to quantify medication concentrations at the level of the threshold/regulatory limit, and not call "positives" below the stated threshold.

4. <u>Urine pH and volume</u>

The pH of the urine (whether the urine is acidic or alkaline) that the horse produces post-race can be a major factor (potentially one hundred- to one thousand-fold or greater pH dependent variability) in determining urinary medication or medication metabolite concentrations and therefore the detection time. While this factor is outside the control of the horseman, it may play an important role in determining the detection time and/or the regulatory significance of a urinary finding. Urine may also be concentrated or diluted, depending on the state of hydration of the horse or the presence of diuretics, which can also affect medication detection times and withdrawal times.

NOTE*:* This potentially very large (one hundred- to one thousand-fold or greater) pH dependent variability in the urinary concentrations of therapeutic medications makes blood testing a much more equitable forensic procedure than urine testing, as set forth in Section 12 above.

5. <u>Route of Administration</u>

Oral administration of medications can prolong withdrawal times. It can take up to five days for pills or tablets to pass through the intestinal tract of a horse; a pill or tablet that breaks down slowly (technically, a prolonged "dissolution time") in the intestinal tract can potentially release medication into a horse's system for up to five days.

PRECAUTION: **Avoid oral administrations close to post.** ***Therapeutic medications that are administered close to post should, where at all possible, be administered intravenously.***

6. <u>Frequency of Medication Use</u>

Repeated or long-term administrations of some medications, especially repeated oral administrations, can greatly extend withdrawal times. Good examples of such medications include isoxsuprine and the acepromazine/phenothiazine family of tranquilizers.

PRECAUTION: Where possible, avoid repeated or prolonged schedules of administration close to post.

NOTE*:* The potential effect of repeated administrations on detection times/withdrawal times is the reason that withdrawal time guidelines must be *linked* to the regulatory threshold, the formulation used, the daily dose, *and the number of doses/days for which the medication is administered* (see AAEP comments on phenylbutazone detection times, 7.3.11). All of these are veterinary matters and, as such, should be specified by appropriately trained and experienced veterinarians, as set forth in Appendix III-B,

7. Presence in the Environment

7.1 Presence in the horse's environment

Any stall that a horse inhabits during a course of therapy will contain variable and at times highly significant concentrations of the medication in question. This has been shown to occur even if the medication is administered parenterally (other than orally). Environmental presence of the medication is obviously much more likely to occur if the medication is administered orally or in the feed at relatively large doses. Isoxsuprine, for example, is notorious in this regard, having been recovered from cobwebs in a treatment stall, but this effect holds, at some level, for all medications. [22, 38, 39, 40]

PRECAUTION: Care should be taken with orally administered medication to ensure that the stall does not come to contain significant amounts of the medication in question or that other horses in the stable do not become exposed to the medication. Move a treated horse to a fresh stall during the withdrawal time period prior to competition to eliminate the possibility of stall or environmental presence of the medication extending the withdrawal time process.

7.2 Contamination of the sample prior to collection

Research with furosemide has unequivocally demonstrated the necessity of drawing the test blood sample on the contra-lateral side from the site of administration. This is because inadvertent extravascular administration of even small volumes of therapeutic medications has the potential to release from these extravascular sites into the jugular vein, giving rise to spuriously high readings from the injection site vein. [41]

PRECAUTION: With the increasing emphasis on blood testing, every effort should be made to ensure that blood samples drawn for regulatory purposes are drawn from the opposite side of the horse from the side on which the administrations were made.

7.3 Post-collection contamination

Post-collection contamination can occur during the collection of urine samples. It usually occurs with prescription medications or environmental or other substances present in the detention barn environment. When it occurs, the principal protection for the horseman is the absence of metabolized forms of the medication in the urine sample; for most substances, the absence of such metabolites is *prima facie* evidence that such post-collection contamination occurred, as it indicates that the substance did not pass "through" the horse's system prior to collection.

NOTE*:* In the event of post-collection contamination, the blood sample may be expected to be negative, a further advantage of blood testing.

8. Time of Last Meal

If medications are administered orally, recent food intake is likely to reduce the peak blood concentration attained and delay the time at which peak blood concentration is reached, as food may interfere with absorption of the medication into the bloodstream.

9. Release Times of the Medication Preparation

Sustained-release preparations[22] for either oral or intramuscular use are specifically formulated to delay release of the medication into the horse's system, thereby extending detection times and withdrawal times.

PRECAUTION: Where possible, avoid sustained-release preparations close to post.

10. Medication Formulation

For any dosage form, even including intravenous (*i.v.*) formulations, variations in the formulation of a medication may result in substantially different withdrawal times. These variations can be quite significant among different oral formulations.

PRECAUTION: Never assume that seemingly similar products from different manufacturers will have the same withdrawal times. This is the reason for the importance of selecting a high-quality standardized formulation for use in "withdrawal time" research.

11. Other Factors

Individual variation between animals (e.g., amount of body fat), the breed and gender of the horse, co-administration of other medications, the health of the horse, and the amount of stress that the horse is subjected to are additional factors that may affect withdrawal times.

12. More Information:

For more detailed information, consult your veterinarian and the appropriate regulatory body for your particular sport and jurisdiction. See also:

12.1. RMTC withdrawal time information: RMTCnet.com, Withdrawal Times

12.2 *EquineSports Veterinary Manual,* by A V van Weezel Errens, Lotlorien BV, The Hague, the Netherlands, 265 pages, Summer 2007. www.equinesports.info. This publication provides information about the most relevant international equestrian competition regulations, regulatory bodies (USEF, ARCI, AQHA, FEI, IFHA, IFAHR, CPMA) and laboratory outcomes (AORC, RMTC, EHSLC) in relation to scientific pharmacokinetic information of more than 150 therapeutic substances used worldwide in competition horses.

12.3. The AAEP's *Guidelines to Drug Detection Times, Vols. 1-3* (American Association of Equine Practitioners, 1999, 2000, 2001).

12.4. *Equine Drugs and Vaccines: A Guide for Owners and Trainers* by Eleanor M. Kellon, V.M.D. (Breakthrough Publications, 1995).

12.5. *Drugs and the Performance Horse* by Thomas Tobin (Springfield, Ill.: Charles C. Thomas, 1981) or relevant publications that may be available in the scientific literature.

12.6. www.thomastobin.com

Appendix II

Definitions

1. "ZERO TOLERANCE" POLICY/ ZERO TOLERANCE:

The term "zero tolerance" is nothing more than a hypothetical zero tolerance policy statement; this is because actual zero tolerance testing is currently unattainable.

Zero tolerance testing is currently unattainable because the current sensitivity of analytical testing stops at about 1 pg/ml or one part per trillion. What this means, as a practical matter, is that current drug and medication testing cannot detect less than about 2 billion molecules (2,000,000,000) per milliliter in a test sample.

While 2,000,000,000 molecules per milliliter sounds like a large number, it should be remembered that a 3-gram dose of phenylbutazone to a horse contains about 6,000,000,000,000,000,000,000 molecules, that is six septillion molecules, an extremely large number of phenylbutazone molecules. This number of molecules administered is actually six times larger than the approximately 1,000,000,000,000,000,000,000 (1 septillion) stars in the known universe. [Google: We believe that there are on the order of 1021 stars in our Universe. If you write that number out, it looks like this: 1,000,000,000,000,000,000,000.]

For the purposes of this document, zero tolerance testing means utilization of the most sensitive and rigorous testing procedures possible for the substance in question, encompassing the full scope and sensitivity of modern analytical technology. As such, the analytical limit defined by zero tolerance policy "testing" is simply the "limit of detection" (LOD) of the most sensitive testing technique available**. Zero tolerance policy testing, therefore, continually increases in sensitivity as analytical methods improve.**

2. PERFORMANCE-ALTERING SUBSTANCE:
For the purposes of this document, a performance-altering substance shall be any ARCI class 1, 2, 3, 4, or 5 substance not identified as a therapeutic medication by the RMTC/ARCI medication rules, an American racing authority, or the AAEP or any substance with no accepted therapeutic use in horses in training or racing, excluding ARCI substances that are endogenous, dietary, or environmental substances

3. SCREENING TEST:
For the purposes of this document, a screening test is a preliminary test that is used to rapidly evaluate whether a sample may or may not contain a prohibited substance. By definition, a screening test is merely suggestive and does not constitute definitive evidence of the presence of the prohibited substance. Thin Layer Chromatography (TLC) and Enzyme-Linked ImmunoSorbent Assay (ELISA) tests are classic examples of

screening tests. By definition, a screening test yields a "presumptive" identification, which presumptive identification may or may not be confirmed.

4. CONFIRMATORY TEST:
For the purposes of this document, a confirmatory test is a definitive chemical test performed under rigorously controlled conditions that unequivocally establishes the presence of the identified substance in the sample in question. Confirmatory tests are optimally independent of and operate on different chemical principles from the screening test. Mass spectrometry is the current basis for most of the confirmatory tests used in equine forensic science. By definition, a confirmatory test, and especially high-quality mass spectral data, is extremely good evidence for the presence of the reported substance.

5. THERAPEUTIC:
For the purposes of this document, therapeutic means "serving to cure or heal or to preserve health." It is derived from the Greek word *therapeuein*, meaning to nurse (Webster's Dictionary, © 1995).

6. THERAPEUTIC MEDICATION:

Ffor the purposes of this document, a therapeutic medication shall be any ARCI class 2, 3, 4, or 5 substance recognized as a therapeutic medication by the RMTC/ARCI medication rules, an American racing authority, or the AAEP and/or any substance "administered by or under the supervision of a veterinarian that supports the health, welfare, and fitness of horses during training and racing or facilitates their safe and humane handling during routine procedures" (draft AAEP definition of therapeutic medication, communicated November 11, 2002, reproduced with the permission of the AAEP). Appendices III-A and III-B contain, respectively, the 2008 RMTC list of approved therapeutic medications and the AAEP list of approved therapeutic medications with standardized therapeutic dosage regimen information.

7. STANDARDIZED THERAPEUTIC DOSAGE REGIMEN:
For the purposes of this document, a standardized therapeutic dosage regimen refers to 1) a defined formulation of a therapeutic medication, administered at 2) a defined daily dose for 3) a defined number of days. These criteria are defined so as to reflect optimal veterinary medical use of the therapeutic medication in veterinary practice. These standardized therapeutic dosage regimens serve to guide practicing and regulatory veterinarians, analytical chemists, pharmacologists, regulators, and other industry professionals across the nation and the world. (See Appendix III-B for a table of standardized therapeutic medication dosage regimens compiled by the Arthur Committee of the AAEP and apparently more recently extended by the RMTC.)

8. TRACE CONCENTRATION:
For the purposes of this document, a trace concentration is defined as a pharmacologically insignificant concentration of the substance in question in the

biological fluid. [5] The term "trace" is well established in the field and is the term used in the pivotal ARCI resolutions in this area, adopted in Oklahoma in April 1995. [5]

9. ENDOGENOUS, DIETARY, OR ENVIRONMENTAL SUBSTANCES:
For the purposes of this document, an endogenous, dietary, or environmental substance shall be any ARCI class 1, 2, 3, 4, or 5 substance produced within or by the horse itself (endogenous) or that may unavoidably become part of the food supply (dietary) and/or environment of horses (environmental).

10. THRESHOLDS /REGULATORY LIMITS:

10.1 THRESHOLD: For the purposes of this document, a threshold/regulatory limit (or "decision level"/"cut-off"/"reporting level") is any defined and published concentration of a specific analyte (the "regulatory analyte") in a biological fluid that defines a regulatory event. Regulatory analyte concentrations greater than the threshold/regulatory limit may initiate regulatory action; concentrations below the threshold/regulatory limit are, in general, of no regulatory interest. The terms "threshold/regulatory limit," "cut-off," "limitation on the sensitivity of testing," "reporting level," and "decision level," are, for all practical purposes, equivalent in regulatory terms, although not necessarily in scientific terms, as set forth below [5]. "Threshold" is the historically established term in this area in North America (see Appendix IX). A current list of available world thresholds/regulatory limits is presented in Appendix VII.

And we now explicitly set forth that for the purposes of this medication policy, all regulatory thresholds should be expressed as concentrations of the specified regulatory analyte in the specified matrix, usually plasma or urine, and be published as an integral part of the jurisdiction's medication rules. Secret, undisclosed, "in-house" thresholds, whether expressed as concentrations in a specified matrix or, as is apparently sometimes the case, in less satisfactory and less scientific formats, as set forth below, are hereby categorically rejected and are not considered to be unambiguously defined or communicated and as such are not acceptable regulatory policy.

10.2 SUBTHRESHOLDS: The term threshold also includes "SUBTHRESHOLDS.". A subthreshold is a secondary threshold for a pharmacologically related medication designed to prevent the calling of a "positive" on a clearly subpharmacological concentration of a trace level of a pharmacologically related medication. For example, the RMTC/ARCI regulatory threshold for phenylbutazone is 5 µg/ml in plasma/serum in many states, and if phenylbutazone is present at/or below this concentration, then no other non-steroidal anti-inflammatory is permitted. However, to prevent application of the zero tolerance policy to irrelevant traces of other non-steroidal anti-inflammatory medications, secondary thresholds, so-called SUBTHRESHOLDS, are required for approved related medications or endogenous, dietary, or environmental substances that may be present at detectable but

subpharmacological concentrations. These secondary thresholds are called subthresholds, and below the secondary or subthreshold, the medication is, for regulatory purposes, not present. The first proposed national subthreshold in place is the RMTC/ARCI rule for phenylbutazone, where the threshold for phenylbutazone is 5 mcg per milliliter, and the subthreshold for phenylbutazone is 1 µg/ml in plasma/serum. Louisiana also recognizes the same 1 µg/ml subthreshold plasma concentration for phenylbutazone but has also adopted subthresholds for flunixin of 2 ng/ml in plasma/serum and ketoprofen of 0.5 ng/ml in plasma/serum.

10.3 THRESHOLD VARIANT: "LIMITATIONS ON THE SENSITIVITY OF TESTING": A somewhat equivalent but scientifically and forensically much less satisfactory approach to the problem of regulatory thresholds is the approach of "limitations" on the sensitively of testing. In this approach, the limit of detection (LOD) of the test is deliberately adjusted so that the test does not "see" concentrations below the estimated threshold, so that the estimated limit of detection of the test becomes the regulatory threshold. The forensic problem with this approach is that the limit of detection of the test, as an experimentally defined value, is not precisely known since determination of the limit of detection is subject to experimental variance, and indeed a limit of detection is always correctly expressed as a mean value, plus or minus the uncertainty of the method. Additionally, the limit of detection may also vary significantly from sample to sample, depending on the characteristics of the matrix. This means that the actual regulatory threshold in place in these jurisdictions is not an absolute stated value, but the experimental result of a process that inevitably shows day-to-day and also sample-to-sample individually and experimentally defined variations.

And in the absence of an explicitly concentration defined regulatory threshold, the actual effective threshold in the jurisdiction question is only approximately known, which creates problems with the forensic interpretation and application of both the primary and referee analysis data.

In sum, the use of a limitation on the sensitively of testing in the place of an explicitly stated concentration threshold increases the uncertainty and opacity of the testing process for therapeutic medications and endogenous, dietary, and environmental substances.

Unless the limit of detection (LOD) of the test is available to the regulated, regulation by limited sensitivity testing is regulation by the use of secret, in-house thresholds that are also experimentally variable and, in regulatory terms, poorly defined.

10.4 THRESHOLD VARIANT: REPORTING LEVELS: In or about the year 2000, our European colleagues introduced the concept of "reporting levels." The term "reporting level" has not been specifically defined; our best attempt at a definition is that a reporting level is a "level" (read "concentration") in blood or urine above which a chemical identification leads to regulatory action and is by definition greater than

the limit of quantification (LOQ) of the method. It remains unclear precisely how these "reporting levels" are defined or communicated between laboratories, between laboratories and regulators, between regulators, and, when the need arises, between scientists.

And unless the actual concentration of the "reporting level" is available to the regulated, regulation by use of in-house reporting levels is regulation by the use of secret, in-house thresholds.

10.5 Threshold "HARMONIZATION": Regulators in Europe and Asia speak of the "harmonization" of testing procedures, including presumably harmonization of the "reporting levels" defined above. To our knowledge, the term "harmonization" is scientifically undefined, and the process is undescribed in the scientific literature.

10.6 THRESHOLD VARIANT: TIME RULES: A "TIME RULE" is a defined time prior to post, usually expressed in hours or days, during which a specified medication may not be administered. A major difficulty with a "time rule" is that the evidence of an infraction is usually an expert opinion as to the time of administration of the medication question and is not an actual quantifiable and independently reproducible parameter such as a regulatory analyte concentration. Time rules, therefore, constitute regulation by expert opinion. As such, time rules are subjective in their interpretation and application and impossible to definitively rebut. Time rules are therefore inherently less objective and scientific than rules based on specified published regulatory thresholds for a defined regulatory analyte in a defined matrix.

11. ANALYTICAL STANDARDS:
For the purposes of this document, analytical standards are of two types: reference standards and internal standards.

11.1) Certified Reference Standards are chemical substances (or medications) of certified high purity (certified reference standards) to which unknowns are compared in order to accurately verify the identity and/or determine the concentration of the substance (the regulatory analyte) to be analyzed. Many unique regulatory analyte certified reference standards for use in racing chemistry have been synthesized and made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

11.2) Internal Standards are chemical substances of certified high purity that are used, by direct addition ("internal standards"), in quantitative analytical procedures to ensure the accuracy of quantitation of an analyte. Among other factors, internal standards are used to correct for losses of an analyte or variations in instrument stability during an analytical procedure. Because **internal** standards are actually added to the test samples, the best, or most appropriate, internal standards are compounds having chemical properties closely similar to the regulatory analyte but analytically distinguishable. In analytical procedures utilizing mass

spectrometry, the best internal standards are most often isotopically labeled versions (very often deuterated analogs) of the regulatory analyte. Internal standards are considered an absolute requirement for accurate quantitative analyses, and many unique regulatory analyte stable isotope internal standards have been synthesized and made available to racing chemists and researchers, courtesy of HBPA-supported research. [6, 8, Appendices IV and V].

11.3) Prior to the HBPA Equine Drug Metabolite Standard Synthesis Program, few if any equine drug metabolite certified reference standards/regulatory analyte standards/internal standards for equine drug metabolites were available to the industry; since then, the HBPA Equine Drug Metabolite standard synthesis program has moved aggressively to fulfill this pressing scientific and regulatory need, as set forth in Appendix IV.

12. WITHDRAWAL TIME GUIDELINES:

12.1: WITHDRAWAL TIME For the purposes of this document, a withdrawal time is a suggested period before an event to cease administration of a medication so as to minimize the risk of post-race detection of a residue of the medication. When estimating a withdrawal time, in a therapeutic context, veterinarians must take numerous factors into account, including but not restricted to the longest known "detection time" for the medication, the dose used, the form in which the medication was/is administered, the route of administration, the number of administrations/duration of treatment, the sensitivity of testing/known detection time, the chemical and pharmacokinetic characteristics of the medication, the appropriate *level of risk to be assumed*, and any unique characteristics of the horse or the event in which the horse in question is participating.

Withdrawal time estimates are almost always significantly longer than the longest reported detection time for the medication and ***can vary from jurisdiction to jurisdiction depending on the testing methodology and/or the specific thresholds/regulatory limits*** employed by the laboratory or the authority.

Withdrawal times should be based on consideration of these and other factors and are best recommended by practicing veterinarians who have a unique knowledge of the physiological characteristics of the horse in question and also their accumulated professional experience with regard to the medication, and the horse in question, and, very importantly, the specific jurisdiction in question.

12.2: WITHDRAWAL TIME and LEVEL OF RISK: Based on the above considerations, it is clear that any withdrawal time recommendation carries a finite level of risk/possibility of error. Additionally, the absolute likelihood of a residue being detected increases in direct proportion to the number of times that a given medication administration occurs and the withdrawal time guideline is applied and the risk of a detection event occurring is assumed.

13. CONCENTRATION ("LEVEL"):

In forensic science, a concentration is the weight, generally expressed on the gram scale as micrograms, nanograms, or picograms, of the substance in question dissolved in a unit volume, usually one milliliter of plasma, serum, or urine.

A **MICROGRAM** (mcg, µg) is one millionth of a gram, **1/1,000,000**. A concentration of 1 microgram per milliliter represents a concentration of one part per million (ppm). For example, the RMTC regulatory threshold for phenylbutazone is 5 mcg per ml (5ug/ml) in plasma/serum (7.3.11), and these concentrations are very easily detectable.

A **NANOGRAM** (ng) is one billionth of a gram, **1/1,000,000,000**. A concentration of 1 nanogram per milliliter represents a concentration of 1 part per billion (ppb). For example, a common regulatory threshold for furosemide is 100 nanograms per ml (ng/ml) in plasma/serum (8.1), and these concentrations are, in general, readily detectable if the chemist knows what he/she is looking for.

To relate one part per billion to everyday life, one part per billion represents one second in your life if you are 32 years of age.

A **PICOGRAM** (pg) is one trillionth of a gram, 1**/1,000,000,000,000**. A concentration of 1 picogram (pg) per milliliter represents a concentration of 1 part per trillion. For example, the CHRB plasma/serum threshold for clenbuterol is 25 picograms per ml (pg/ml) of plasma/serum (7.2.4). Current analytical technology in equine forensic science can detect medications down to the low picogram level.

Obviously, following the point of reference established above, one part per trillion represents one second in your life if you are 32,000 years of age.

And a 1 pg/ml concentration of a medication contains about 2 billion molecules of the average therapeutic medication.

A **FEMTOGRAM (fg)** is one quadrillionth of a gram, **1/1,000,000,000,000,000**. A concentration of 1 femtogram per milliliter represents a concentration of 1 part per quadrillion. To date, we are unaware of any regulatory thresholds or "positive calls" at femtogram levels, but they are entirely legal and possible under zero tolerance policies.

Following the point of reference established above, one part per quadrillion represents one second in your life if you are 32,000,000, that is 32 million years of age.

An **ATTOGRAM (ag)** is one quintillionth of a gram, **1/1,000,000,000,000,000,000**. A concentration of 1 attogram per milliliter represents a concentration of 1 part per quintillion. We are unaware of any regulatory thresholds or "positive "calls at femtogram levels, but they are entirely legal and possible under zero tolerance policies.

One part per quintillion represents one second in your life if you are 32,000,000,000, 000, that is 32 billion years of age, that is more than twice the approximately 13 billion year age of the universe.

And 50,000 carbon atoms weigh approximately 1 attogram, so about 2,000 medication molecules of a 300 molecular weight medication will weigh one attogram.

A **ZEPTOGRAM (zg)** is one sextillionth of a gram, **1/1,000,000,000,000,000,000,000**. A concentration of 1 zeptogram per milliliter represents a concentration of 1 part per quintillion. We are unaware of any regulatory thresholds or "positive "calls at zeptogram levels, but they are entirely legal and possible under zero tolerance policies.

Measuring at zeptogram/ml concentrations, we are now approaching "zero" drug molecules since two medication molecules of molecular weight 300 will weigh approximately 1 zeptogram.

Obviously, following the points of reference established above, one part per sextillion represents one second in your life if you are 32,000,000,000,000, that is 32 trillion years of age or, in other words more than two thousand times the approximately 13 billion year age of the universe.

A point of clarification: While concentration is the correct scientific term, some technical journals (clinical journals) and most lay publications speak of blood or urinary "levels," which are equivalent to blood or urinary "concentrations."

14. LINKED:

For the purposes of this document, with reference to a withdrawal time guideline, the term "linked/scientifically linked" means that the withdrawal time guideline is based on published scientific research that specifies 1) the medication formulation used, 2) the dose and route of administration, 3) the frequency and duration of administration, 4) the measured rate of decline of the concentration of the regulatory analyte in the forensic sample being analyzed, 5) the relevant threshold/regulatory limit, 6) the complete population distribution of the analyte values at the withdrawal time, and 7) the best statistical estimate of the uncertainty associated with any withdrawal time guideline presented. To date the only withdrawal time guideline scientifically linked to a regulatory threshold is that for furosemide, as determined in HBPA-supported research performed at the University of Kentucky in the early 1980s [37]. In the 2003 iteration of this document, this concept was described by the word "keyed."

15. REGULATORY ANALYTE:
For the purposes of this document, the regulatory analyte refers to the specific analyte identified and, where appropriate, quantified for regulatory purposes in the forensic sample. The regulatory analyte may be the parent material or medication presented to the horse, or a metabolite, or a portion of a metabolite of the material identified in or

recovered from the forensic sample. For example, 2-(hydroxyethyl) promazine sulfoxide, the regulatory analyte for acepromazine, is a chemically modified form of acepromazine, 2-(hydroxyethyl) promazine sulfoxide recovered from the urine sample after glucuronide hydrolysis of the major equine urinary metabolite of acepromazine, 2-(hydroxyethyl) promazine sulfoxide glucuronide. Unless otherwise specified, the regulatory analyte is the analyte defined in the rules on which regulatory action is based and, for the purposes of thresholds/regulatory limits, the regulatory analyte is the only analyte quantified. [6, 8, Appendices IV and V]

16. TESTING LABORATORY:
For the purposes of this document, a testing laboratory is a laboratory employed by or under contract to a racing authority that meets the criteria set forth by the National Forensic Science Technology Center (NFSTC), American Association for Laboratory Accreditation (A2LA) or International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17025, as presented in Appendix VI.

17. VALIDATED METHOD:
For the purposes of this document, a validated method is a qualitative or quantitative analytical method that has been rigorously characterized and tested in more than one laboratory *for the specific substance in question* so that it meets the accreditation requirements of the accrediting body and performs as described in the Standard Operating Procedure[23] (SOP).

18. QUANTITATIVE TEST:
For the purposes of this document, a quantitative test is a test that both unequivocally identifies and accurately defines the concentration of the prohibited substance in the test sample.

19. MEASUREMENT UNCERTAINTY:

For the purposes of this document, the result of any measurement of the concentration of a substance is simply *an estimate of the true or actual value*. Therefore, the result is complete only when accompanied by a quantitative statement of the uncertainty of the estimate, (e.g., a confidence interval) as established by appropriate statistical methods.

20. 95% CONFIDENCE LIMIT:
For the purposes of this document, the 95% confidence interval is a range of concentration values within which 95% of all measurements will fall. In order for a "positive" to be called, the lower limit of the 95% confidence interval for a determined concentration must be greater than the threshold/regulatory limit.

21. DETECTION TIME:
For the purposes of this document, a detection time is an officially or scientifically reported period of time after administration during which a medication, or a metabolite

thereof or the regulatory analyte, has been detected in the blood, urine, or other body fluid of a horse.

Until recently, detection times were almost always based on results obtained in experimental situations with small numbers of horses that were not actually racing. These limitations must be kept in mind when extrapolating from reported detection times to actual withdrawal time guidelines.

Good sources of detection time information include the AAEP *Guidelines for Drug Detection Times* and the Canadian, Australian, and European guides to detection times summarized in "An Overview of the Effective World Rules on Therapeutic Medications," available from the Gluck Equine Research Center. [42]

22. SUSTAINED-RELEASE PREPARATIONS:
Many therapeutic medications are formulated as sustained- or controlled- release preparations. These formulations are typically administered orally or intramuscularly, and the therapeutic medication is then slowly released from the formulation.

Slow release of the medication serves the very useful purpose of prolonging its therapeutic effect. It also, however, prolongs the detection time of the medication and other substances used in the administered formulation. Procaine penicillin is a typical sustained-release formulation, administered intramuscularly, in which the prolonged release of procaine, a substance used in the formulation, has become a regulatory problem for horseracing.

23. STANDARD OPERATING PROCEDURE:
For the purposes of this document, a Standard Operating Procedure (SOP) is a complete description of an analytical method or procedure, prepared to the required standards of the accrediting body, that enables its confident replication in the hands of an appropriately trained and equipped individual.

Appendix III-A

RMTC Therapeutic Medications Routinely Used and Identified as Necessary by the Veterinary Advisory Committee

This table is reproduced courtesy of Dr. Scot Waterman and the Racing Medication and Testing Consortium. For each of these therapeutic medications, the RMTC is developing appropriate regulatory thresholds in plasma or urine and also associated withdrawal time guidelines [Communicated January 2008].

First Priority Group (Currently in Research)

1. Acepromazine
2. Butorphanol
3. Detomidine
4. Glycopyrrolate
5. Lidocaine
6. Mepivacaine
7. Methocarbamol
8. Pyrilamine

Second Priority Group

9. Boldenone
10. Stanozolol
11. Testosterone
12. Dantrolene
13. Dexamethasone
14. Fluphenazine
15. Hydroxyzine
16. Nandrolone

Third Priority Group

17. Albuterol
18. Betamethasone
19. Diclofenac
20. Methylprednisolone
21. Reserpine
22. Triamcinolone
23. Trichlormethiazide
24. Xylazine

Fourth Priority Group

25. Atropine
26. Beclomethasone
27. Buscopan
28. Cromolyn
29. Isoxsuprine
30. Pentoxyfylline
31. Phenytoin
32. Prednisolone

Fifth Priority Group

33. Diazepam
34. Dipyrone
35. Fluorprednisolone
36. Guaifenesin
37. Isoflupredone
38. Prednisone

Research Already Under Way

39. Aminocaproic Acid
40. Carbazochrome
41. Clenbuterol
42. Procaine Penicillin

Already in Body of Model Rules

43. Cimetidine
44. DMSO
45. Flunixin
46. Furosemide
47. Ketoprofen
48. Omeprazole
49. Phenylbutazone
50. Ranitidine

Appendix III-B

American Association of Equine Practitioners' Therapeutic Medications List, 2007

An American Association of Equine Practitioners "Therapeutic Medication Committee" under the chairmanship of Dr. Rick Arthur has created this therapeutic medication list. The most recent iteration is below with dosage, route of administration, frequency of administration, clinical use, and clinical "cut-off' information. This table is reproduced courtesy of Dr. Rick Arthur and the American Association of Equine Practitioners.

An earlier iteration of this AAEP therapeutic medication list was generated by circulating a list of several hundred medications to AAEP members and asking them to indicate which agents they routinely used in their practice. The data were collected and reviewed by the AAEP and presented for publication as Appendix G in the Proceedings of the "Testing for Therapeutic Medications, and Environmental and Dietary Substances in Racing Horses, " pp. 191-192, 1995, Lexington, Ky. [3, 5]

MEDICATION	CLASS	DOSAGE	ROUTE OF ADMIN.	FREQ. OF ADMIN.	CLINICAL USE	PRIORITY	CLINICAL CUT-OFF
ACEPROMAZINE	3	15 MG	IV	SID	TRANQUILIZER	H	48 HRS (72-24 HRS)
ACETYLSALICYLIC ACID (ASPIRIN)	4	60 GRAIN	PO	SID	NSAID ANTI-PLATELET	L	24 HRS
ALBUTEROL	3	6 PUFFS	INHALER (MDI)	BID	BRONCHODILATOR	H	24 HRS
AMINOCAPROIC ACID	4	2500-5000 MG	IV	SID	ANTI-FIBRINOLYTIC (EIPH)	L	24 HRS
ATROPINE	3	9 MG OPHTHALMIC OINTMENT	INTRA-SYNOVIAL TOPICAL	ONCE SID	CHRONIC SYNOVITIS MYDRAISIS	M	48 HRS
BECLOMETHASONE	4	3 - 6 PUFFS	INHALER (MDI)	BID	STEROIDAL ANTI-INFLAMMATORY	L	24 HRS
BETAMETHASONE	4	6-30 MG	IA	ONCE	STEROIDAL ANTI-INFLAMMATORY	L	48 HRS
BOLDENONE	4	125-500 MG	IM	ONCE/ 2-3 WEEKS	ANABOLIC	L	48 HRS

BUTORPHANOL	3	2-10 MG	IV	ONCE	TRANQUILIZER	H	48 HRS
CIMETIDINE	5	8-20 MG/KG	PO	BID OR TID	H_2 BLOCKER (GASTRIC ULCERS)	L	24 HRS
CLENBUTEROL	3	O.8 MCG/KG	PO	BID	BRONCHODILATOR	H	96 HRS*
CROMOLYN	5	20-40 MG	NEBULIZER MDI	SID	MAST CELL STABILIZER	L	24 HRS
DANTROLENE	4	300-500 MG	PO	SID	EXERTIONAL MYOSITIS	H	48 HRS
DETOMIDINE	3	2-10 MG	IV, IM	ONCE	TRANQUILIZER	H	48 HRS
DEXAMETHASONE	4	5-40 MG	IV, PO, IM	SID	STEROIDAL ANTI-INFLAMMATORY	M	24 HRS
DIAZAPAM	2	20-30 MG	IV	SID	TRANQUILIZER/ SEDATIVE	L	72-120 HRS
DMSO	5	.1 MG/KG	IV, PO	SID	ANTI-INFLAMMATORY	L	24 HRS
DIPYRONE	4	5-10 GM	IV	SID	ANTI-PYRETIC SPASMOLYTIC	L	72 HRS
FLUNIXIN	4	250-500 MG	IV	SID	NSAID	L	24 HRS
FLUPHENAZINE	2	10-30 MG	IM	ONCE/ 1-2 WEEKS	LONG-ACTING TRANQUILIZER	H	7+ DAYS
FLUORO-PREDNISOLONE	4	2-20 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	L	48 HRS
GUAIFENESIN	4	DOSAGE VARIABLE (ORAL PREPS)	PO	SID, BID	EXPECTORANT	L	48 HRS
HYDROXYZINE	2	250-500 MG	PO	BID	CHRONIC URTICARIA	H	72 HRS
IBUPROFEN	4	4-10 GMS	PO	BID	NSAID	L	24 HRS
ISOFLUPREDONE	4	10-20 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	L	48 HRS
ISOXSUPRINE	4	200-400 MG	PO	BID	PERIPHERAL VASODILATOR	L	48 HRS
KETOPROFEN	4	1000 MG	IV	SID	NSAID	L	24 HRS
LIDOCAINE	2	UP TO 200 MG	SQ	ONCE	LOCAL ANESTHETIC	H	48 HRS
MECLOFENAMIC ACID	4	500-1000 MG	PO	BID	NSAID	L	24 HRS
MEPIVACAINE	2	UP TO 50 MG	SQ	ONCE	LOCAL ANESTHETIC	H	48 HRS

METHOCARBAMOL	4	2-5 GMS 5-20 GMS	IV, PO	SID, BID BID, TID	CENTRALLY ACTING MUSCLE RELAXATION	H	24 HRS 48 HRS
METHYL-ERGONOVINE	4	5-10 MG	IV, IM	SID	EIPH	L	24 HRS
METHYL-PREDNISOLONE	4	40-200 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	M	48 HRS
NANDROLONE	4	100-200 MG	IM	ONCE/ 1-2 WEEKS	ANABOLIC STEROID	L	48 HRS
NAPROXEN	4	4-5 GM	PO	SID, BID	NSAID	L	24 HRS
OMEPRAZOLE	5	2.2 GM	PO	SID	PROTON PUMP INHIBITOR (GASTRIC ULCERS)	L	24 HRS
PENTOXIYFYLLINE	4	2-4 GMS	PO	BID	PERIPHERAL VASOLDILATOR	M	48 HRS
PHENYTOIN	4	3-5 GMS	PO	SID	EXERTIONAL MYOSITIS	H	48 HRS
PHENYLBUTAZONE	4	1-2 GMS	IV, PO	SID, BID	NSAID	L	24 HRS
PREDNISOLONE	4	100-500 MG	IV, IM	SID	STEROIDAL ANTI-INFLAMMATORY	L	24 HRS
PREDNISONE	4	200-400 MG	IM, PO	SID, BID	STEROIDAL ANTI-INFLAMMATORY	L	24 HRS
PROCAINE (AS PEN-G)	3	20 MG/ML PROCAINE (≈ 30 ML)	IM	BID	PROCAINE-LOCAL ANESTHETIC (PPG-ANTIBIOTIC)	H	48 HRS
RANITIDINE	5	8 MG/KG	PO	BID	H_2 BLOCKER (GASTRIC ULCERS)	L	24 HRS
RESERPINE	2	2.5 MG	IM	ONCE/ 2-3 WEEKS	LONG ACTING TRANQUILIZER	H	7+ DAYS
STANOZOLOL	4	250-500 MG	IM	ONCE/ 1-3 WEEKS	ANABOLIC STEROID	L	48 HRS
TESTOSTERONE	4	500-1000 MG	IM	ONCE/ 1-3 WEEKS	ANABOLIC STEROID	L	48 HRS
TRIAMCINOLONE	4	2-18 MG	IA, IM	ONCE	STEROIDAL ANTI-INFLAMMATORY	L	24 HRS
TRICHLOR-METHIAZIDE	4	200-400 MG	PO	SID	DIURETIC (COMBINED W/ DEXAMETHASONE AS NAQUSONE)	L	24 HRS
XYLAZINE	3	100-400 MG	IV, IM	ONCE	TRANQUILIZER	H	48 HRS

* Clenbuterol could have a 48-hr CLINICAL CUTOFF, but 96 hrs was generally thought to be clinically workable.

Appendix IV

Equine Medication and Medication Metabolite Standards Synthesized: The HBPA Equine Drug/ Metabolite Standard Synthesis Program

As set forth throughout this document, most urinary identifications of therapeutic medications are based on the detection of specific urinary metabolites or urinary metabolite fragments of the medication, herein specified as the regulatory analyte. Until recently, reference standards for few if any of these unusual urinary regulatory analytes were available to racing chemists and researchers. Starting in 1995, and supported by the National and local Horsemen's Benevolent & Protective Associations, the Kentucky Equine Drug Council, and the University of Kentucky, and, more recently, the Kentucky Science and Engineering Foundation (KSEF) and in association with the Neogen Corp. and, again more recently, with ChemPharma of Richmond, Kentucky, a chemical synthesis program (The HBPA Equine Drug/ Metabolite Standard Synthesis Program) has been instituted to make these regulatory analytes/certified reference standards/stable isotope internal standards available to racing chemists and the racing industry worldwide.

Since 2000, blood/plasma testing has become an increasingly important regulatory approach. Blood/plasma testing almost always involves the detection of parent medication, and the appropriate certified reference standard is generally the parent medication, with a requirement for a stable isotope internal standard of the parent medication. For example, the HBPA program has synthesized and provided racing chemists and racing industry researchers stable isotope internal standards for phenylbutazone as deuterated phenylbutazone, for furosemide as deuterated furosemide and for clenbuterol as deuterated clenbuterol and others, as set forth below.

The left hand column of the table below lists the parent therapeutic medication, while the right hand column lists the deuterated reference standard/metabolite/regulatory analyte as the specific chemical name of the regulatory analyte/standard.

	Parent Medication	Regulatory Analyte/Internal Standard
1	Acepromazine [deuterated metabolite]	Deuterated 2-(1-hydroxyethyl) promazine sulfoxide
2	Acepromazine [metabolite]	(1-hydroxyethyl) promazine (uncrystallized)
3	Acepromazine [metabolite]	Acepromazine sulfoxide
4	Amitraz [deuterated metabolite]	D_6-N-2,4-Dimethylphenyl-N'-methylformamidine [D_6]
5	Bupivacaine [metabolite]	3-hydroxybupivacaine
6	Chlorpromazine [metabolite]	7-hydroxychlorpromazine
7	Clenbuterol [deuterated	Deuterated Clenbuterol [D_9]

	standard]	
8	Clenbuterol [metabolite]	1-(4-Amino-3,5-Dichlorophenyl)ethane-1,2-diol
9	Clenbuterol [metabolite]	2-[2-)4-Amino-3,5-Dicholorophenyl)-2-hydroxyethylamino]-2-Methyl-Propan-1-Ol
10	Colterol and Bitolterol [metabolite]	3-O-Methylcolterol
11	Detomidine [deuterated metabolite]	Deuterated carboxydetomidine [D_4]
12	Detomidine [metabolite]	Carboxydetomidine
13	Fluphenazine [metabolite]	7-hydroxyfluphenazine
14	Furosemide [deuterated standard]	Deuterated Furosemide [D_5]
15	Flunixin [deuterated standard]	Deuterated Flunixin [D_3]
16	Guafenesin [deuterated standard]	Deuterated Guafenesin [D_4]
16	Guanabenz [metabolite]	Hydroxyguanabenz
17	Ketoprofen '[deuterated standard]	Deuterated Ketoprofen [D_4]
18	Lidocaine [deuterated metabolite]	Deuterated 3-hydroxylidocaine [D_4]
19	Lidocaine [metabolite]	3-hydroxylidocaine
20	Mazindol [metabolite]	2-(2-Aminoethyl)-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydro-isoindol-1-one
21	Mepivacaine [deuterated metabolite]	3-hydroxymepivacaine
22	Mepivacaine [metabolite]	3-hydroxymepivacaine [D_3]
23	Methocarbamol [deuterated metabolite]	Deuterated Methocarbamol [D_4]
24	Phenylbutazone [deuterated metabolite]	Deuterated Phenylbutazone [D_9]
25	Procaine [deuterated metabolite]	Deuterated Procaine [D_{10}]
26	Promazine [metabolite]	3-hydroxypromazine
27	Promethazine [metabolite]	Promethazine sulfoxide
28	Propanolol [metabolite]	4-hydroxypropanolol
29	Propiomazine [metabolite]	2-(1-hydroxypropyl) promethazine sulfoxide
30	Propionylpromazine [metabolite]	2-(1-hydroxypropyl) promazine sulfoxide
31	Pyrilamine [deuterated standard]	Deuterated Pyrilamine [$C_{13}D_3$]
32	Pyrilamine [metabolite]	O-desmethylpyrilamine
33	Ropivacaine [metabolite]	3-hydroxyropivacaine
34	Ropivacaine [metabolite]	4-hydroxyropivacaine

35	Selegiline [metabolite]	Desmethylselegiline
36	Tramadol [metabolite]	Desmethyltramadol
38	Tripelennamine [metabolite]	3-OH-Tripelennamine

Appendix V

National and Local Horsemen's Benevolent and Protective Associations That Have Supported Equine Medication Research at the Maxwell H. Gluck Equine Research Center

National HBPA
Mr. Joe Santanna, President
4063 Iron Works Pike, Ste. 2
Lexington, KY 40511-8905

Canada HBPA
Mr. Mel Snow, President
609 West Hastings Street, Suite 888
Vancouver, BC, Canada
V6B 4W4

Florida HBPA
Mr. Samuel Gordon, President
P.O. Box 1808
Opa-Locka, FL 33055

Nebraska HBPA
Mr. Jerry Fudge, President
6406 South 150th Street
Omaha, NE 68137

Kentucky HBPA
Mr. Rick Hiles, President
3733 S. Fourth Street
Louisville, KY 40214

Ontario HBPA
Ms. Sue Leslie, President
135 Queen's Plate Drive, Suite 370
Rexdale, Ontario, Canada
M9W 6V1

Indiana HBPA
Mr. Randy Klopp, President
6348 Behner Reach
Indianapolis, IN 46250

Charles Town HBPA
Mr. Raymond J. Funkhouser, President
P.O. Box 581
Charles Town, WV 25414

Ohio HBPA
Mr. Jim Yaegel, President
3684 Park Street
Grove City, OH 43123

Arkansas HBPA
Dr. Earl Bellamy, President
P.O. Box 1670
Hot Springs, AR 71902

Michigan HBPA
Mr. Rick McCune, President
4800 South Harvey
Muskegon, MI 49444-9762

Pennsylvania HBPA
Mr. Joe Santanna, President
P.O. Box 88
Grantville, PA 17028

Alabama HBPA
Mr. Skip Drinkard, President
1523 Indian Hills Road, N.E.
Hartselle, AL 35640

Arizona HBPA
Mr. Michael Napier, President
P.O. Box 43636
Phoenix, AZ 85080

Louisiana HBPA
Mr. Sean Alfortish, President
1535 Gentilly Boulevard
New Orleans, LA 70119

Oklahoma HBPA
Mr. Joe Lucas, President
1 Remington Place
Racing Office Bldg. 427-87
Oklahoma City, OK 73111

Tampa Bay Downs HBPA
Mr. Bob Jeffries, President
P.O. Box 1768
Oldsmar, FL 34677

Washington HBPA
Mr. Frank McDonald, President
3702 W. Valley Highway N., Ste. 210
Auburn, WA 98001

Mountaineer Park HBPA
Mr. Charles E. Bailey, President
P.O. Box 358
Chester, WV 26034

Iowa HBPA
Mr. Leroy Gessmann, President
1 Prairie Meadows Drive
Altoona, IA 50009

Minnesota HBPA
Mr. Tom Metzen, President
1100 Canterbury Road
Shakopee, MN 55379

Oregon HBPA
Mr. Jim Fergason, President
10350 N. Vancouver Way
Portland, OR 97217

Texas Horsemen's Partnership
Dr. Tommy Hays
Mr. Larry Christopher, Chairman
P.O. Box 142533
Austin, TX 78714

Appendix VI

Laboratory Standards*

In order to receive accreditation under National Forensic Science Technology Center (NFSTC), American Association for Laboratory Accreditation (A2LA), or International Standards Organization (ISO)/International Electrotechnical Commission (IEC) 17025, laboratories must meet a series of minimum requirements. These standards include the following:

• The laboratory must have a suitably qualified technical leader having either a four-year baccalaureate with college credit courses in chemistry, pharmacology, and toxicology or related subjects, course work in statistics, and five years of experience as an analytical chemist in a laboratory analyzing substances in body fluids, including experience in giving evidence, or a graduate degree with college credit courses in chemistry, pharmacology, and toxicology or related subjects, course work in statistics, and two years of experience as an analytical chemist in a laboratory analyzing substances in body fluids, including experience in giving evidence.

• The laboratory must demonstrate that it has effective systems in place to manage information collection, analysis, and dissemination.

• The laboratory shall maintain a list of all analysts, the tests they are authorized to perform, and the reports they are authorized to sign.

• All authorized analysts must have successfully completed a competency test before being allowed to perform unsupervised analyses and sign reports.

• The laboratory must prepare a list of critical reagents, which are those materials utilized in analyses which can determine the accuracy of testing and the non-functioning of which would result in significant loss of sample. All critical reagents must be shown to be of suitable quality before being released for routine use.

• The laboratory must be able to establish and maintain the forensic integrity of samples. Samples must be received, identified, have their receipt recorded, and be stored under conditions that protect them from loss, contamination, and deleterious change.

• All analytical data, including quality control data, manual data transfers, calculations, chain of custody records, and conclusions must be verified by another authorized analyst.

• All equipment and laboratory apparatus, the performance of which could affect the quality of test results, must be calibrated and maintained at appropriate intervals. The calibration status of all equipment must be clearly noted on or by that equipment.

• The laboratory must have measures to ensure that the incidence of false negative results is kept to a minimum.

* Courtesy of the National Forensic Science Technology Center, 2002.

APPENDIX VII: INTERNATIONAL THRESHOLDS/REGULATORY LIMITS (updated July, 2008)

The table below shows the substances for which thresholds/regulatory limits have been established in certain racing jurisdictions. The thresholds/regulatory limits are expressed in terms of concentrations (ng/ml) in particular body fluids. The reference number at the right indicates where the information about a particular substance was found. Consult the references section at the end of this appendix and or the relevant authority website.

"THRESHOLDS/ REGULATORY LIMITS"

	MEDICATION	CONCENTRATION	FLUID	JURISDICTION	REF #
1	Acepromazine	10 ng/ml	urine	Ohio	1
	Acepromazine	25 ng/ml	urine	California	2
	Acepromazine	25 ng/ml	urine	Washington	3
	Acepromazine	25 ng/ml	urine	New Mexico	4
	Acepromazine	25 ng/ml	urine	Louisiana	8
2	Albuterol	1 ng/ml	plasma	Louisiana	8
	Albuterol	1 ng/ml	plasma	Oklahoma	41
	Albuterol	1 ng/ml	urine	California	2
	Albuterol	1 ng/ml	urine	New Mexico	4
	Albuterol	1 ng/ml	urine	Washington	3
	Albuterol	5 ng/ml	urine	Louisiana	8
3	Arsenic	200 ng/ml	urine	Texas	5
	Arsenic	300 ng/ml	urine	International	6
4	Atropine	10 ng/ml	urine	California	2
	Atropine	10 ng/ml	urine	New Mexico	4
	Atropine	70 ng/ml	urine	Oklahoma	41
	Atropine	75 ng/ml	urine	Louisiana	8
5	Benzocaine	50 ng/ml	urine	California	2
	Benzocaine	50 ng/ml	urine	Washington	3
	Benzocaine	50 ng/ml	urine	New Mexico	4
6	BZE* (Benzoylecgonine)	50 ng/ml	urine	unattributed	7
	BZE (Benzoylecgonine)	50 ng/ml	urine	Washington	40
	BZE (Benzoylecgonine)	100 ng/ml	urine	Florida	3
	BZE	150 ng/ml	urine	Illinois	14

	(Benzoylecgonine)				
	BZE (Benzoylecgonine)	150 ng/ml	urine	Ohio	1
	BZE (Benzoylecgonine)	150 ng/ml	urine	Louisiana	8
	BZE (Benzoylecgonine)	150 ng/ml	urine	Oklahoma	41
	BZE (Benzoylecgonine)	<1ng/ml	plasma	Louisiana	8
7	Betamethasone	60 ng/ml	urine	Ohio	1
8	Boldenone	15 ng/ml (intact males only)	urine	ARCI	39
	Boldenone	< 200 pg/ml	plasma	Pennsylvania (interim)	12
	Boldenone	15 ng/ml (intact males only)	urine	Delaware	31
	Boldenone	15 ng/ml (intact males only)	urine	International	6
	Boldenone	15 ng/ml (intact males only)	urine	California	2
	Boldenone	15 ng/ml (intact males only)	urine	Indiana	
	Boldenone	15 ng/ml (intact males only)	urine	Virginia	30
9	Bupivacaine	5 ng/ml	urine	Ohio	1
	Bupivacaine	5 ng/ml	urine	Washington	3
10	Butorphanol	10 ng/ml	urine	Ohio	1
11	Caffeine	250 ng/ml	serum	Canada	9
	Caffeine	1,000 ng/ml	urine	Canada	9
	Caffeine	10 ng/ml	plasma	Hong Kong	10
	Caffeine	10 ng/ml	plasma	Jockey Club of Brasileiro	11
	Caffeine	30 ng/ml	urine	Hong Kong	10
	Caffeine	100 ng/ml	urine	Oklahoma	41
	Caffeine	100 ng/ml	urine	Ohio	1
	Caffeine	100 ng/ml	urine	Louisiana	8
	Caffeine	200 ng/ml	urine	Florida	33
	Caffeine	25 ng/ml	plasma	Louisiana	8
	Caffeine	100 ng/ml	plasma	Washington	3
	Caffeine	100 ng/ml	plasma	Oregon	22
	Caffeine	100 ng/ml	plasma	Maryland	23
	Caffeine	100 ng/ml	plasma	Nebraska	24

12	Carbon Dioxide	36 millimoles/L	plasma	International	6
13	Clenbuterol	0.5 ng/ml	plasma	Louisiana	8
	Clenbuterol	15 ng/ml	urine	Louisiana	8
	Clenbuterol	1 ng/ml	plasma	Oklahoma	41
	Clenbuterol	1 ng/ml	urine	Ohio (1999)	1
	Clenbuterol	25 pg/ml	plasma	Kentucky	21
	Clenbuterol	25 pg/ml	plasma	Washington	3
	Clenbuterol	25 pg/ml	plasma	California	2
	Clenbuterol	5 ng/ml	urine	California	2
	Clenbuterol	5 ng/ml	urine	New Mexico	4
14	Dantrolene	100 ng/ml	plasma	Ohio (1999)	1
	Dantrolene	100 ng/ml	plasma	Oklahoma	41
15	Dexamethasone	60 ng/ml	urine	Ohio (1999)	1
	Dexamethasone	100 ng/ml	urine	Louisiana	8
	Dexamethasone	3 ng/ml	plasma	USEF	15
16	Diclofenac	5 ng/ml	plasma	Kentucky	21
	Diclofenac	5 ng/ml	plasma	Oklahoma	41
	Diclofenac	5 ng/ml	plasma	USEF	15
17	Dimethylsulfoxide	500,000 ng/ml	urine	Illinois	14
	Dimethylsulfoxide	10,000 ng/ml	urine	Ohio (1999)	1
	Dimethylsulfoxide	10,000 ng/ml	plasma	Kentucky	21
	Dimethylsulfoxide	10,000 ng/ml	plasma	Oregon	22
	Dimethylsulfoxide	15,000 ng/ml	urine	International	6
	Dimethylsulfoxide	1,000 ng/ml	plasma	International	6
	Dimethylsulfoxide	1,000 ng/ml	plasma	Oklahoma	41
18	Dipyrone	1,000 ng/ml	plasma	Oklahoma	
	Dipyrone	1,000 ng/ml	plasma	Jockey Club of Brasileiro	11
19	Eltenac	100 ng/ml	plasma	USEF	15
20	Firocoxib	240 ng/ml	plasma	USEF	15
21	Flumethasone	10 ng/ml	urine	Ohio (1999)	1
22	Flunixin	20 ng/ml	plasma	RMTC National (2007)	10
	Flunixin	1,000 ng/ml	plasma	USEF	15
	Flunixin	1,000 ng/ml	plasma	Idaho	13
	Flunixin	1,000 ng/ml	plasma	New Mexico	4
	Flunixin	500 ng/ml	plasma	Colorado	25
	Flunixin	250 ng/ml	plasma	Oklahoma	41

	Flunixin	50 ng/ml	plasma	California	2,2a
	Flunixin	50 ng/ml	plasma	Louisiana	8
	Flunixin	25 ng/ml	plasma	Oregon	22
	Flunixin	20 ng/ml	plasma	Arkansas	26
	Flunixin	20 ng/ml	plasma	Illinois	14
	Flunixin	20 ng/ml	plasma	Indiana	43
	Flunixin	20 ng/ml	plasma	Kansas	27
	Flunixin	20 ng/ml	plasma	Ohio (200X)	
	Flunixin	20 ng/ml	plasma	Washington	3
	Flunixin	20 ng/ml	plasma	Kentucky	21
	Flunixin	20 ng/ml	plasma	Minnesota	28
	Flunixin	20 ng/ml	plasma	Maryland	23
	Flunixin	20 ng/ml	plasma	Iowa	29
	Flunixin	20 ng/ml	plasma	Virginia	30
	Flunixin	10 ng/ml	plasma	Pennsylvania	12
	Flunixin	40 ng/ml	plasma	Sweden	
	[Flunixin Subthreshold]	2 ng/ml	plasma	Louisiana	8
23	Furosemide	100 ng/ml	plasma	RMTC National (2007)	10
	Furosemide	80 ng/ml	plasma	Idaho	13
	Furosemide	50 ng/ml	plasma	Oklahoma	41
	Furosemide	100 ng/ml	plasma	Others	
	Furosemide	100 ng/ml	plasma	Jockey Club of Brasileiro	11
	Furosemide	100 ng/ml	plasma	Illinois	14
	Furosemide	100 ng/ml	plasma	Indiana	43
	Furosemide	100 ng/ml	plasma	Texas	5
	Furosemide	100 ng/ml	plasma	Oregon	22
	Furosemide	100 ng/ml	plasma	California	2
	Furosemide	100 ng/ml	plasma	Kentucky	21
	Furosemide	100 ng/ml	plasma	Minnesota	28
	Furosemide	100 ng/ml	plasma	Delaware	31
	Furosemide	100 ng/ml	plasma	Maryland	23
	Furosemide	100 ng/ml	plasma	Washington	3
	Furosemide	100 ng/ml	plasma	Arkansas	26
	Furosemide	100 ng/ml	plasma	Kansas	27
24	Glycopyrrolate	5 ng/ml	urine	Ohio	1
25	Hydrocortisone	1,000 ng/ml	urine	Ohio	1
	Hydrocortisone	1,000 ng/ml	urine	International	6
26	Ibuprofen	100 ng/ml	serum	Kentucky	21
27	Imipramine	20 ng/ml	plasma	Jockey Club of Brasileiro	11

28	Indomethacin	50 ng/ml	plasma	Jockey Club of Brasileiro	11
29	Isoflupredone	60 ng/ml	urine	Ohio (1999)	1
30	Isoxsuprine	1,000 ng/ml	urine	Illinois	14
	Isoxsuprine	1,000 ng/ml	urine	Ohio (1999)	1
31	Ketoprofen	10 ng/ml	plasma	RMTC National (2007)	10
	Ketoprofen	250 ng/ml	plasma	USEF	15
	Ketoprofen	100 ng/ml	plasma	Oklahoma	41
	Ketoprofen	10 ng/ml	plasma	Ohio	
	Ketoprofen	50 ng/ml	plasma	New Mexico	4
	Ketoprofen	10 ng/ml	plasma	California	2
	Ketoprofen	10 ng/ml	plasma	Arkansas	26
	Ketoprofen	10 ng/ml	plasma	Illinois	14
	Ketoprofen	10 ng/ml	plasma	Indiana	43
	Ketoprofen	10 ng/ml	plasma	Kansas	27
	Ketoprofen	10 ng/ml	plasma	Louisiana	8
	Ketoprofen	10 ng/ml	plasma	Washington	3
	Ketoprofen	10 ng/ml	plasma	Oregon	22
	Ketoprofen	10 ng/ml	plasma	Kentucky	21
	Ketoprofen	10 ng/ml	plasma	Minnesota	28
	Ketoprofen	10 ng/ml	plasma	Colorado	25
	Ketoprofen	10 ng/ml	plasma	Iowa	29
	[Ketoprofen Subthreshold]	0.5 ng/ml	plasma	Louisiana	8
32	Lidocaine	25 ng/ml	plasma	Jockey Club of Brasileiro	11
	Lidocaine	<1 ng/ml	plasma	Louisiana	8
	Lidocaine	50 ng/ml	urine	Ohio (1999)	1
	Lidocaine	50 ng/ml	urine	Washington	3
	Lidocaine	25 ng/ml	urine	Louisiana	8
	Lidocaine	25 ng/ml	urine	Oklahoma	41
33	Meclofenamic Acid	1,000 ng/ml	plasma	Ohio (1999)	1
	Meclofenamic Acid	1,000 ng/ml	plasma	Kentucky	21
	Meclofenamic Acid	1,000 ng/ml	plasma	New Mexico	4
	Meclofenamic Acid	2,500 ng/ml	plasma	USEF	15
	Meclofenamic Acid	1,000 ng/ml	plasma	Idaho	13
34	Mephenesin	200 ng/ml	plasma	Jockey Club of Brasileiro	11
35	Mepivacaine	5 ng/ml	urine	Ohio (1999)	1
	Mepivacaine	10 ng/ml	urine	California	2
	Mepivacaine	10 ng/ml	urine	Washington	3
	Mepivacaine	10 ng/ml	urine	New Mexico	4

	Mepivacaine	25 ng/ml	urine	Louisiana	8
36	Methocarbamol	1,000 ng/ml	plasma	Ohio (1999)	1
	Methocarbamol	1,000 ng/ml	plasma	Oklahoma	41
	Methocarbamol	4,000 ng/ml	plamsa	USEF	15
37	Methoxytyramine	4,000 ng/ml	urine	International	6
38	Methylprednisolone	1,000 ng/ml	urine	Ohio (1999)	1
39	Morphine	120 ng/ml	urine	Louisiana	8
	Morphine	100 ng/ml	urine	Oklahoma	41
	Morphine	50 ng/ml	urine	England, Webbon	16
	Morphine	50 ng/ml	urine	Ohio (1999)	1
	Morphine	50 ng/ml	urine	Washington	3
	Morphine	<1 ng/ml	plasma	Louisiana	8
40	Naproxen	40,000 ng/ml	plasma	USEF	15
	Naproxen	10,000 ng/ml	plasma	Ohio	1
	Naproxen	5,000 ng/ml	plasma	Idaho	13
	Naproxen	750 ng/ml	plasma	Oklahoma	41
41	Nandrolone	1 ng/ml (geldings, fillies and mares)	urine	Indiana	43
	Nandrolone	1 ng/ml (geldings, fillies and mares)	urine	Virginia	30
	Nandrolone	1 ng/ml (geldings, fillies and mares)	urine	ARCI	39
	Nandrolone	1 ng/ml (geldings, fillies, and mares)	urine	Delaware	31
	Nandrolone	1 ng/ml (geldings, fillies, and mares)	urine	California	2
	Nandrolone	45 ng/ml (intact males only)	urine	ARCI	39
	Nandrolone	45 ng/ml (intact males only)	urine	Indiana	43
	Nandrolone	45 ng/ml (intact males only)	urine	Virginia	30
	Nandrolone	45 ng/ml	urine	Washington	42
	Nandrolone	45 ng/ml (intact males only)	urine	California	2

	Nandrolone	< 200 pg/ml	plasma	Pennsylvania (interim)	12
42	Oxyphenbutazone	5,000 ng/ml	plasma	North America, ARCI	17, 39
	Oxyphenbutazone	5,000 ng/ml	plasma	Arizona	32
	Oxyphenbutazone	5,000 ng/ml	plasma	Arkansas	26
	Oxyphenbutazone	5,000 ng/ml	plasma	Florida	33
	Oxyphenbutazone	5,000 ng/ml	plasma	Kansas	27
	Oxyphenbutazone	5,000 ng/ml	plasma	Illinois	14
	Oxyphenbutazone	5,000 ng/ml	plasma	Ohio (1999)	1
	Oxyphenbutazone	5,000 ng/ml	plasma	Louisiana	8
	Oxyphenbutazone	5,000 ng/ml	plasma	Montana	34
	Oxyphenbutazone	5,000 ng/ml	plasma	Idaho	13
	Oxyphenbutazone	5,000 ng/ml	plasma	New Mexico	4
	Oxyphenbutazone	5,000 ng/ml	plasma	Colorado	25
	Oxyphenbutazone	5,000 ng/ml	plasma	Iowa	29
	Oxyphenbutazone	5,000 ng/ml	plasma	West Virginia	35
	Oxyphenbutazone	5,000 ng/ml	plasma	Michigan	36
	Oxyphenbutazone	2,000 ng/ml	plasma	Delaware	31
	Oxyphenbutazone	2,000 ng/ml	plasma	Pennsylvania	12
	Oxyphenbutazone	165,000 ng/ml	urine	Louisiana	8
	Oxyphenbutazone	165,000 ng/ml	urine	Montana	34
	Oxyphenbutazone	165,000 ng/ml	urine	West Virginia	35
43	Pentazocine	50 ng/ml	urine	Ohio (1999)	1
44	Phenylbutazone	5,000 ng/ml	plasma	North America, ARCI	17, 39
	Phenylbutazone	700 ng/ml	plasma	Jockey Club of Brasileiro	11
	Phenylbutazone	2,000 ng/ml	plasma	Pennsylvania	12
	Phenylbutazone	2,000 ng/ml	plasma	Maryland	23
	Phenylbutazone	2,500 ng/ml	plasma	Delaware	31
	Phenylbutazone	5,000 ng/ml	plasma	Arizona	32
	Phenylbutazone	5,000 ng/ml	plasma	Arkansas	26
	Phenylbutazone	5,000 ng/ml	plasma	Illinois	14
	Phenylbutazone	5,000 ng/ml	plasma	Indiana	43
	Phenylbuazone	5,000 ng/ml	plasma	Kansas	27
	Phenylbutazone	5,000 ng/ml	plasma	Florida	33
	Phenylbutazone	5,000 ng/ml	plasma	Louisiana	8
	Phenylbutazone	5,000 ng/ml	plasma	Texas	5
	Phenylbutazone	5,000 ng/ml	plasma	California	2
	Phenylbutazone	5,000 ng/ml	plasma	New Mexico	4
	Phenylbutazone	5,000 ng/ml	plasma	Idaho	13
	Phenylbutazone	5,000 ng/ml	plasma	Washington	3
	Phenylbutazone	5,000 ng/ml	plasma	Oregon	22
	Phenylbutazone	5,000 ng/ml	plasma	Michigan	36
	Phenylbutazone	5,000 ng/ml	plasma	Iowa	29
	Phenylbutazone	5,000 ng/ml	plasma	Colorado	25

	Phenylbutazone	5,000 ng/ml	plasma	Kentucky	21
	Phenylbutazone	5,000 ng/ml	plasma	Minnesota	28
	Phenylbutazone	5,000 ng/ml	plasma	Montana	34
	Phenylbutazone	5,000 ng/ml	plasma	Oklahoma	41
	Phenylbutazone	5,000 ng/ml	plasma	Virginia	30
	Phenylbutazone	5,000 ng/ml	plasma	West Virginia	35
	Phenylbutazone	5,000 ng/ml	plasma	Wyoming	37
	Phenylbutazone	15,000 ng/ml	plasma	USEF	15
	Phenylbutazone	165,000 ng/ml	urine	Louisiana	8
	Phenylbutazone	165,000 ng/ml	urine	Idaho	13
	Phenylbutazone	165,000 ng/ml	urine	Massachusetts	38
	Phenylbutazone	165,000 ng/ml	urine	Montana	34
	Phenylbutazone	165,000 ng/ml	urine	West Virginia	35
	[Phenylbutazone Subthreshold]	1,000 ng/ml	plasma	Louisiana	8
45	Prednisolone	1,000 ng/ml	urine	Ohio (1999)	1
46	Prednisone	100 ng/ml	urine	Ohio (1999)	1
47	Procaine	750 ng/ml	urine	Hong Kong	18
	Procaine	5 ng/ml	plasma	Louisiana	8
	Procaine	25 ng/ml	plasma	Canada	9
	Procaine	25 ng/ml	plasma	Oklahoma	41
	Procaine	100 ng/ml	plasma	Jockey Club of Brasileiro	11
	Procaine	50 ng/ml	urine	Ohio (1999)	1
	Procaine	50 ng/ml	urine	Louisiana	8
	Procaine	10 ng/ml	urine	California	2
	Procaine	25 ng/ml	urine	Washington	3
	Procaine	10 ng/ml	urine	New Mexico	4
48	Promazine	20 ng/ml	plasma	Jockey Club of Brasileiro	11
	Promazine	50 ng/ml	urine	Ohio (1999)	1
	Promazine	25 ng/ml	urine	California	2
	Promazine	25 ng/ml	urine	Washington	3
	Promazine	25 ng/ml	urine	New Mexico	4
49	Pyrilamine	5 ng/ml	plasma	Jockey Club of Brasileiro	11
	Pyrilamine	50 ng/ml	plasma	Oklahoma	41
	Pyrilamine	50 ng/ml	urine	Washington	3
	Pyrilamine	50 ng/ml	urine	Ohio	
50	Salicylates	750,000 ng/ml	urine	California	2
	Salicylates	750,000 ng/ml	urine	Washington	3
	Salicylates	750,000 ng/ml	urine	Ohio (1999)	1

	Salicylates	750,000 ng/ml	urine	New Mexico	4
51	Salicylic Acid	750,000 ng/ml	urine	Ohio (1999)	1
	Salicylic Acid	750,000 ng/ml	urine	International	6
	Salicylic Acid	6,500 ng/ml	plasma	International	6
	Salicylic Acid	750,000 ng/ml	urine	Texas	5
	Salicylic Acid	65,000 ng/ml	plasma	Oklahoma	41
52	Scopolamine	75 ng/ml	urine	Louisiana	8
53	Stanozolol (16β-hydroxystanozolol)	1 ng/ml	urine	ARCI	39
	Stanozolol (16β-hydroxystanozolol	1 ng/ml	urine	California	2
	Stanozolol (16β-hydroxystanozolol)	< 200 pg/ml	plasma	Pennsylvania	12
	Stanozolol (16β-hydroxystanozolol)	1 ng/ml	urine	Indiana	43
	Stanozolol (16β-hydroxystanozolol)	1 ng/ml	urine	Virginia	30
54	Strychnine	100 ng/ml	urine	Oklahoma	41
	Strychnine	100 ng/ml	urine	Louisiana	8
55	Sulfa Drugs	1,000 ng/ml	urine	Oregon	22
56	Terbutaline	10 ng/ml	urine	Ohio (1999)	1
57	Testosterone (epitestosterone)	20 ng/ml (geldings)	urine	International, ARCI	6, 39
	Testosterone (epitestosterone)	20 ng/ml (geldings)	urine	California	2
	Testosterone (epistestosterone)	20 ng/ml (geldings)	urine	Indiana	43
	Testosterone (epitestosterone)	20 ng/ml (geldings)	urine	Virginia	30
	Testosterone (epitestosterone)	55 ng/ml (fillies and mares)	urine	International, ARCI	6, 39
	Testosterone (epitestosterone)	55 ng/ml (fillies and mares)	urine	California	2

	Testosterone (epitestosterone)	55 ng/ml (fillies and mares)	urine	Indiana	43
	Testosterone (epitestosterone)	55 ng/ml (fillies and mares)	urine	Virginia	30
	Testosterone (epitestosterone)	< 200 pg/ml (fillies and geldings)	plasma	Pennsylvania	12
58	Tetramisole	80 ng/ml	plasma	Jockey Club of Brasileiro	11
59	Theobromine	2,000 ng/ml	urine	Ohio (1999)	1
	Theobromine	2,000 ng/ml	urine	USEF	6
	Theobromine	2,000 ng/ml	urine	Texas	5
	Theobromine	2,000 ng/ml	urine	Washington	3
	Theobromine	400 ng/ml	urine	Florida	33
60	Theophylline	400 ng/ml	urine	Florida	33

*BZE is the major urinary metabolite of cocaine.

For comparative purposes, the "thresholds" for human urine concentrations, as established by the Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (SAMHSA), are listed below [19, 20].

NB: The SAMHSA opiate testing cutoff concentrations were increased, effective December 1, 1998, from 300 ng/ml to 2,000 ng/ml.

INITIAL DRUG TEST LEVEL (IN URINE)

	(ng/ml)
Marijuana metabolites	50
Cocaine metabolites	300
Opiate metabolites	2000
Phencyclidine	25
Amphetamines	1000

CONFIRMATORY DRUG TEST LEVEL (IN URINE)

	(ng/ml)
Marijuana metabolite[1]	15
Cocaine metabolite[2]	150
Opiates	
Morphine	2000
Codeine	2000
6-Acetylmorphine[3]	10
Phencyclidine	25

Amphetamines	
Amphetamine	500
Methamphetamine[4]	500

[1]Delta-9-tetrahydrocannabinol-9-carboxylic acid.
[2]Benzoylecgonine.
[3]Test for 6-AM when the morphine concentration is greater than or equal to 2000 ng/ml.
[4]Specimen must also contain amphetamine at a concentration greater than or equal to 200 ng/ml.

Note: The urinary threshold's for marijuana and cocaine are specified as "metabolite" and the specific metabolites analyzed, the "regulatory analytes" are defined in the footnotes.

References for Appendix VII:

1) **The Ohio State Racing Commission**
Drug Classification System (June, 1999)
The Ohio State University
Analytical Toxicology Laboratory
College of Veterinary Medicine
Columbus, OH 43210
Communicated summer 1999 by Mr. Tom Journell, Esq.

2) **California Horse Racing Board**
Horsemen's Handbook Concerning Medication Rules and Regulations
1010 Hurley Way, Suite 300
Sacramento, CA 95825
http://www.chrb.ca.gov/

2a) **Memorandum from California Horse Racing Board re: NSAID rule changes 5/19/99**

3) **Washington Horse Racing Commission**
7912 Martin Way, Suite D
Olympia, WA 98516
http://www.whrc.wa.gov/

4) **New Mexico Racing Commission**
300 San Mateo Boulevard, N.E., Suite 110
Albuquerque, NM 87108
(505) 841-6400
Title 15, Chapter 2, Part 6

5) **Texas Racing Commission**
Medication Information
8505 Cross Park Drive, Suite 110
Austin, TX 78758
http://www.txrc.state.tx.us/

6) **International Federation of Horseracing Authorities**
Des Autoripes Hippiques
De Courses Au Galop
46, place Abel Gance
92655 Boulogne Cedex
France
http://www.horseracingintfed.com/

7) **Australian Equine Veterinarian Association**
Detection of Therapeutic Substances in Racing Horses
134-136 Hampden Road
Artarmon NSW 2064
Australia
http://www.eva.org.au/

8) **Equine Medication Surveillance Lab**
School of Veterinary Medicine
Louisiana State University
Baton Rouge, LA 70803

9) **Canadian Pari-Mutuel Agency Schedule of Drugs**
Canadian Pari-Mutuel Agency
P.O. Box 5904
Station F
Ottawa, Ontario
K2C 3X7
Canada
http://www.cpma-acpm.gc.ca/cpma_e.html

10) **Testing for Therapeutic Medications, Environmental and Dietary Substances in Racing Horses** A workshop held at the Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, KY, August 18-19, 1994. pp. 85-91

11) **Jockey Club of Brasileiro**
Laboratorio Anti-doping
Rua Bartolomeu Mirte, 1314 - Gavea
Rio de Janeiro
Brazil

12) **Pennsylvania State Horse Racing Commission**
Guidelines for Medications in Racehorses
Agriculture Building
2301 North Cameron Street
Harrisburg, PA 17110-9408

13) **1998 Idaho Administrative Code.**
IDAPA 11/04/01. Department of Law Enforcement, Rules Governing Horse Racing.

14) **Illinois Administrative Code**
Ch.1 § 603, Subtitle B, Subchapter C.

15) **USA Equestrian (formerly American Horse Shows Association)**
4047 Iron Works Parkway
Lexington, KY 40511
(859) 258-2472

16) **Substances of Dietary Origin: Morphine**
Ginn, A., Clark, A., Grainger, L., Houghton, E., Williams, R.B.* Horseracing Forensic Laboratory, Newmarket Road, Fordham, Cambridgeshire, England, CB7 5WW; *42 Portman Square, London, England, W1H 0EN.

17) **American Association of Equine Practitioners**
Policy on Therapeutic Medications in Racehorses
4075 Iron Works Parkway
Lexington, KY 40511
http://www.aaep.org/

18) **Hong Kong Jockey Club**
Racing Laboratory
Sha Tin
Hong Kong
http://www.hkjc.com/english/index.asp

19) **Department of Health and Human Services:**
Substance Abuse and Mental Health Services Administration
"SAMHSA's Mandatory Guidelines for Federal Workplace Drug Testing Programs": http://www.health.org/workplace/GDLNS-94.htm

20) **Department of Health and Human Services:**
Substance Abuse and Mental Health Services Administration
"SAMHSA's Mandatory Guidelines for Federal Workplace Drug Testing Programs: Federal Register Notice Changing the Opiate Testing Cutoff Concentrations (effective December 1, 1998)"
http://www.health.org/workplace/testing.htm

21) **Kentucky Horse Racing Authority**
4063 Ironworks Pkwy
Building B
Lexington, KY 40511
http://www.khra.ky.gov

22) **Oregon Racing Commission**
800 NE Oregon St.. Suite 310
Portland, OR 97232
http://www.racing.oregon.gov

23) **Maryland Racing Commission**
300 E. Towsontowne Boulevard
Towson, Maryland 21286
http://www.dllr.state.md.us/racing

24) **Nebraska State Racing Commission**
PO Box 95014
301 Centennial Mall South,
6th Floor Lincoln, NE 68509-5014
http://www.horseracing.state.ne.us

25) **Colorado Department of Revenue**
Division of Racing Events
Lakewood Office
1881 Pierce Street Suite 108
Lakewood, Colorado 80214
http://www.revenue.state.co.us

26) **Arkansas Racing Commission**
1515 West Seventh Street Suite 505
Little Rock, AR 72201
http://www.arkansas.gov/dfa/racing/rc_index.html

27) **Kansas Racing and Gaming Commission**
700 SW Harrision, Suite 420
Topeka, KS 66603
http://www.ksracing.org

28) **Minnesota Racing Commission**
P.O. Box 630
Shakopee, MN 553709
http://www.mnrace.commission.state.mn.us

29) **Iowa Racing and Gaming Commission**
717 East Court, Suite B

Des Moines, IA 50309
http://www.iowa.gov/irgc

30) **Virginia Racing Commission**
10700 Horsemen's Road
New Kent, Virginia 23124
http://www.vrc.virginia.gov

31) **Delaware Department of Agriculture**
Thoroughbred Racing Division
2320 South DuPont Highway
Dover, Delaware 19901
http://www.dda.delaware.gov/thoroughbred

32) **Arizona Department of Racing**
1110 West Washingtonk, Suite 260
Phoenix, AZ 85007
http://www.azracing.gov

33) **Florida Division of Pari-Mutuel Wagering**
1940 North Monroe Street
Tallahasse, FL 32399
http://www.myflorida.com/dbpr/pmw

34) **Montana Board of Horse Racing**
Department of Livestock
Horse Racing Bureau
301 S. Park
Helena, Montana 59620
http://www.mt.gov/liv/horseracing

35) **West Virginia Racing Commission**
P.O. Box 551
Charlestown, WV 25414
http://www.wvf.state.wv.us/racing

36) **Michigan Racing Commissioner**
P.O. Box 30773
Lansing, MI 48909
http://www.michigan.gov/horseracing

37) **Wyoming Pari-Mutuel Commission**
2515 Warren Avenue, Suite 301
Cheyenne, WY 82002
http://www.parimutuel.state.wy.us

38) **Massachusetts Racing Commission**
One Ashburton Place, Room 1313
Boston, MA 02018
http://www.state.ma.us/src/

39) **Association of Racing Commissioners International**
2343 Alexandria Dr., Suite 200
Lexington, KY 40504
http://www.arci.com

40) **Camargo F, Hughes C, Lehner A, Stirling K and Tobin T:** "Trace" Benzoylecgonine Identifications in Post-Race Urines: Probable Sources and Regulatory Significance of Such Identifications. AAEP Proceedings, 52:331-336, 2006.

41) **Oklahoma Horse Racing Commission**
Directive on Commission-Sanctioned Thresholds [3A:205.2(H)]
Approved by Commission of 1/25/07
Shepherd Mall
2401 NW 23rd. street, Suite 78
Oklhahoma City, OK 73107
http://www.ohrc.org

42) **Dehennin L, Bonnaire Y, Plou P:** Detection of nandrolone administratin to the entire male horse by a provisional concentration threshold for urinary oestranediol determine by gas chromatography-mass spectrometry. *Equine Vet J*, 39(2):186-188, 2007.

43) **Indiana Horse Racing Commission**
150 W. Market Street #530
Indianapolis, IN 46204
(317) 233-3119

Appendix VIII

Literature Cited

1. McKinsey & Company, Inc.: Building a World-Class Drug Detection System for the Racing Industry: A National Strategic Plan. Published May, 1991.

2. Racing Integrity and Drug Testing Task Force Report. Published by the National Thoroughbred Racing Association, 2001.

3. Tobin T, Mundy GD, Stanley SD, Sams RA, Crone D (Eds): Testing for Therapeutic Medications, Environmental and Dietary Substances in Racing Horses, Proceedings of Workshop, Lexington, Ky., August 1994. Published 1995. [KY Ag Exp Sta #95-14-058]

4. Tobin T: Fifties rules, nineties testing: The need for thresholds for therapeutic medications. *Racing Update*, **18** (10): 89-92, 1995.

5. Tobin T, Harkins JD, Sams RA: Testing for therapeutic medications: Analytical/pharmacological relationships and "limitations" on the sensitivity of testing for certain agents. *J Vet Pharmacol Therap*, **22:**220-233, 1999. [KY Ag Exp Sta #98-14-134]

6. Karpiesiuk W, Lehner A, Woods WE, Tobin T: *Equine Drug Metabolites and Standards*. Booklet published by Gluck Equine Research Center, Lexington, Ky., 1998.

7. Short CR, Sams RA, Soma LR, and Tobin T: The regulation of drugs and medicines in horses racing in the United States. The Association of Racing Commissioners International Uniform Classification of Foreign Substances Guidelines. *J Vet Pharmacol Therap*, **21:**144-153, 1998.

8. Harkins JD, Lehner A, Karpiesiuk W, Woods WE, Dirikolu L, Boyles J, Carter WG, Tobin T: Bupivacaine in the horse: Relationship of local anaesthetic responses and urinary concentrations of 3-hydroxybupivacaine. *J Vet Pharmacol Therap*, **22:**181-195, 1999. [KY Ag Exp Sta #98-14-166]

9. Harkins JD, Mundy GD, Woods WE, Lehner A, Karpiesiuk W, Rees WA, Dirikolu L, Bass S, Carter WG, Boyles J, Tobin T: Lidocaine in the horse: Its pharmacological effects and their relationship to analytical findings. *J Vet Pharmacol Therap*, **21:**462-476, 1998. [KY Ag Exp Sta #97-14-71]

10. Dirikolu L, Lehner AF, Karpiesiuk W, Harkins JD, Woods WE, Carter WG, Boyles J, Fisher M, Tobin T: Identification of lidocaine and its metabolites in post-administration equine urine by ELISA and MS/MS. *J Vet Pharmacol Therap*, **23:**215-222, 2000. [KY Ag Exp Sta #00-14-91]

11. Harkins JD, Karpiesiuk W, Woods WE, Lehner AF, Mundy GD, Rees WA, Dirikolu L, Bass S, Carter WG, Boyles J, Tobin T: Mepivacaine: Its pharmacological effects and their relationship to analytical findings in the horse. *J Vet Pharmacol Therap*, **22:**107-121, 1999. [KY Ag Exp Sta #98-14-148]

12. Woods WE, Lehner A, Karpiesiuk W, Boyles J, Carter WG, Harkins JD, Tobin T: Detection and quantitation of 3-hydroxymepivacaine in horse urine. *Proc 12th Int'l Conf Racing Analysts Vets*, Vancouver, Canada, 1998, pp 324-328. [KY Ag Exp Sta #98-14-35]

13. Lehner AF, Harkins JD, Karpiesiuk W, Woods WE, Robinson NE, Dirikolu L, Fisher M, Tobin T: Clenbuterol in the horse: Confirmation and quantitation of serum clenbuterol by LC-MS-MS after oral and intra-tracheal administration. *J Anal Toxicol*, **25:**280-287, 2001. [KY Ag Exp Sta #00-14-122]

14. Soma LR, Uboh CE, Guan F, Luo Y, Teleis D, Runbo L, Birks EK, Tsang DS, Habecker P. Tissue distribution of clenbuterol in the horse. *J Vet Pharmacol Ther*, **27**(2):91-8, 2004.

15. Soma LR, Uboh CE, Guan F, Moate P, Luo Y, Teleis D, Li R, Birks EK, Rudy JA, Tsang DS: Pharmacokinetics and disposition of clenbuterol in the horse. *J Vet Pharmacol Ther*, **27**(2):71-7, 2004.

16. Harkins JD, Mundy GD, Stanley SD, Woods WE, Boyles J, Arthur RA, Sams RA, Tobin T: Regulatory significance of procaine residues in plasma and urine samples: A preliminary communication. *Equine Vet J*, **28:**121-125, 1996.

17. Pennsylvania State Horse Racing Commission: "Guidelines for Medications in Racehorses." Agriculture Building, 2301 North Cameron St., Harrisburg, PA 17110-9408.

18. Sams RA, Gerken DF, Detra RL, Ault K, Harkins JD, Woods WE, Karpiesiuk W, Lehner AF, Fisher M, Tobin T: Pyrilamine in the horse: I. Isolation, identification and synthesis of its major urinary metabolite. Manuscript in preparation, 2001.

19. Harkins JD, Woods WE, Lehner AF, Karpiesiuk W, Hughes C, Gates RS, Fisher M, Tobin T: Pyrilamine in the horse: II. Detection and pharmacokinetics of pyrilamine and its major urinary metabolite. Manuscript in preparation, 2001.

20. Woods WE, Harkins JD, Lehner AF, Dirikolu L, Karpiesiuk W, Boyles J, Carter WG, Fisher M, Heller T, Tobin T: Detection and disposition of pyrilamine and its urinary metabolite O-desmethylpyrilamine in equine blood and urine: A preliminary report. Submitted to *Proc 13th Int'l Conf Racing Analysts Vets*, Cambridge, UK, 2000. [KY Ag Exp Sta #00-14-85]

21. Canadian Pari-Mutuel Agency Schedule of Drugs. Published by Canadian Pari-Mutuel Agency, P.O. Box 5904, Station F, Ottawa, Ontario, Canada K2C 3X7.

22. The Racing Appeals Board of Racing Victoria Limited ACN 096 917 930; Reasons for decision in the matter of the appeal by the owners of Mistegic against the decision of the stewards to disqualify Mistegic from the Schillaci Stakes pursuant to Rule of Racing AA 177. Date of determination: March 21, 2002.

23. Liebman D: Brass Hat Disqualified From Second in Dubai World Cup. *Bloodhorse***.** Posted May 3, 2006.

24..Sams, R.A., "Guidelines for Drug Detection Times." The American Association of Equine Practitioners, 4075 Iron Works Pike, Lexington, KY, 40511, November 1999.

25. Anderson D, Kollias-Baker C, Colahan P, Keene RO, Lynn RC, Hepler DI: Urinary and serum concentrations of diclofenac after topical application to horses. *Vet* Ther, **6**(1):57-66, 2005.

26. Tobin T: *Trace Level Benzoylecgonine Identifications in Post-Race Urines: Probable Sources and the Regulatory Significance of Such Identifications*, HBPA Booklet published by Gluck Equine Research Center, Lexington, Ky., 2000.

27. Camargo FC, Hughes C, Lehner AF, Stirling K, Tobin T: "Trace" benzoylecgonine identifications in post-race urines: Probable sources and regulatory significance of such identifications. *Proc 52nd Annual Conf AAEP*, San Antonio, Texas, December 2006, pp 331-337.

28. Harkins JD, Rees WA, Mundy GD, Stanley SD, Tobin T: An overview of the methylxanthines and their regulation in the horse. *Equine Practice*, **20:**10-16, 1998. [KY Ag Exp Sta #96-14-084]

29. Budhraja A, Camargo FC, Hughes C, Lehner AF, Stirling K, Brennan N, Dowling M, Tobin T: Caffeine and theobromine identifications in post-race urines: Threshold levels and regulatory significance of such identifications. *Proc 53nd Annual Conf AAEP*, Orlando, Fla., December 2007, pp 87-94.

30. Combie J, Blake JW, Ramey BE, Tobin T: The pharmacology of narcotic analgesics in the horse: Quantitative detection of morphine in equine blood and urine and logit-log transformations of this data. *Am J Vet Res* **42**(9): 1523-1530, 1981.

31. Ginn A, Clark A, Grainger L, Houghton E, Williams RB: Substances of dietary origin: Morphine. *Proc 13th Int'l Conf Racing Analysts Vets*, Cambridge, UK, 2000, p 184.

32. Camargo FC, Lehner AF, Karpiesiuk W, Stirling K, Kavanagh PV, Brennan N, Dowling M, Tobin T: Review of environmental morphine identifications: Worldwide occurrences and responses of authorities. *Proc 51st Annual Convention of the American Association of Equine Practitioners,* Seattle, Wash., December 2005, pp. 58-64.

33. Department of Health and Human Services: Substance Abuse and Mental Health

Services Administration, "SAMHSA's Mandatory Guidelines for Federal Workplace Drug Testing Programs." http://www.health.org/workplace/GDLNS-94.htm

34. Department of Health and Human Services: Substance Abuse and Mental Health Services Administration "SAMHSA's Mandatory Guidelines for Federal Workplace Drug Testing Programs: Federal Register Notice Changing the Opiate Testing Cutoff Concentrations (effective December 1, 1998)."
http://www.health.org/workplace/testing.htm

35. Dyke TM, Sams RA: Detection and determination of theobromine and caffeine in urine after administration of chocolate-coated peanuts to horses. *J Anal Toxicol*, **22**(2):112-6, 1998.

36. "Uniform Classification Guidelines for Foreign Substances and Recommended Penalties and Model Rule," Association of Racing Commissioners International, revised July 2007.

37. Chay S, Woods WE, Rowse K, Nugent TE, Blake JW, Tobin T: The pharmacology of furosemide in the horse. V. Pharmacokinetics and blood levels of furosemide after intravenous administration. *Drug Metab Disp*, **11**(3):226-231, 1983.

38. Russell CS and Maynard S: Environmental contamination with isoxsuprine. *Proc 13th Int'l Conf Racing Analysts Vets*, Cambridge, UK, 2000, pp 381-383.

39. Norgren A, Ingvast-Larsson C, Kallings P, Fredriksson E and Bondesson U: Contamination and urinary excretion of flunixin after repeated administration in the horse. Proc 13th Int'l Conf Racing Analysts Vets, Cambridge, UK, 2000, pp 377-380.

40 Wennerlund I, Ingvast-Larsson C, Kallings P, Fredriksson E and Bondesson U: Pharmacokinetics and urinary excretion of naproxen after repeated oral administration in the horse. Proc 13th Int'l Conf Racing Analysts Vets, Cambridge, UK, 2000, pp 195-200.

41. Furosemide in the Horse: Its Actions, Effects, and Regulatory Control. *Proceedings of a Testing Integrity Program Workshop and Seminar,* New Orleans Hilton Riverside, March 1, 1998, 124 pp., Wind Publications, 2000.windpub.com/booklist.htm

42. Carter WG, Troppmann A, Franklin B, Stirling K, and Tobin T: *An Overview of the Effective World Rules on Therapeutic Medications: A Work in Progress*. Booklet available from the Gluck Equine Research Center, November 2002 or at www.thomastobin.com.