An Overview of the EffectiveWorld Rules on Therapeutic Medications

A Work in Progress

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2) Executive Summary

The goal of this booklet is to summarize the current effective world medication rules, with a view toward understanding, comparing and harmonizing them.

To that end, Section 3, **Background**, describes the approaches to medication control that have been developed to date, and sets forth the widely-articulated need for "*limitations*" on the sensitivity of testing for therapeutic medications. Section 4, **Definitions**, details the terms used throughout this booklet and in the literature, so that we may analyze the various approaches to this problem. Section 5, **Factors Affecting "Withdrawal Times"**, communicates the complexity of the problem by articulating what must be taken into account when estimating a "*withdrawal time*".

Tables 1-6 detail the medication guidelines that have been established in certain jurisdictions, and it should be understood that these are apparently subject to change at any time. **Table 7** details the Association of Official Racing Chemists' "*performance specifications*." These are considered the minimum detection capability that a laboratory should be capable of, but should not be perceived as, and are not in any way limits on, the sensitivity of testing for the listed agents.

At least three major approaches to the problem of medication control have evolved, none of which is entirely satisfactory: 1) quantitative "*thresholds*"; 2) "*detection times*"; 3) "*withdrawal time guidelines."* Of these, quantitative "*thresholds*" are, in scientific and regulatory terms, the most satisfactory solution.

Quantitative "*thresholds*" or "*limits*" or "*decision levels*" or "*reporting levels*" are, by definition, standard worldwide, and can be related directly to the scientific literature. These "thresholds," however, must ultimately be translated into useful "*withdrawal time guidelines*" for practical application by veterinarians and horsemen.

"*Detection times*" have been published by a number of jurisdictions around the world. These data have been generated by their analytical groups and are often specific to these analytical groups; they are essentially <u>local</u> solutions to the problem. This approach lacks the scientific rigor of the quantitative "*thresholds*" approach, as "*detection time*" data cannot be readily related to the scientific literature.

"*Withdrawal time guidelines*," useful to practitioners but complex in their development, have been established in some jurisdictions. These range from "*official withdrawal times*" to "*suggested withdrawal times*" and are influenced by many factors, as described in Section 5. The actual field "*withdrawal times*" used by practitioners in a number of jurisdictions are detailed in **Tables 3-6**. Where the data are available, we have also included the dose information associated with these "*withdrawal times*." These "*practioners' withdrawal times*" are the effective medication rules in place around the world today.

3) Background and Approaches to Medication Control

In 1903, when the English Jockey Club made the medication of racing horses an offense against the rules of racing, very few medications were detectable. Today, virtually all medications administered to racing horses are readily detectable, and some for long periods after their pharmacological effects are over.

In 1991 the McKinsey Report, a definitive review of medication control commissioned by the Jockey Club, assigned high priority to the establishment of *"threshold levels"* for *"drugs"* [read therapeutic medications] permitted in animals on race day. Specifically, the McKinsey Report stated that,

"the industry should develop test specifications, especially bottom cut-off sensitivity levels, to reduce positives that are not meaningful."

Shortly thereafter, in 1995, the Association of Racing Commissioners International (ARCI) adopted a resolution (ARCI National Conference, Oklahoma City, OK, April 1995), the final two paragraphs of which read as follows:

> *"The Association of Racing Commissioners International strongly recommends that its membership adopt a policy that all chemical findings in official test samples undergo a documented review process by the official veterinarian or appropriate veterinary consultant prior to the initiation of any regulation action. And, further, the ARCI recommends that its members specifically implement procedures to have an official veterinarian or veterinary consultant review findings for ARCI class 4 and 5 substances to address "trace" level detection so as not to lead to disciplinary action based on pharmacologically insignificant "traces" of these substances*."

Echoing this theme, the European Horseracing Scientific Liaison Committee (EHSLC) in its 1997 "Veterinary Drug Detection Times" booklet points out that the

> *"three central reasons for having rules to control the use of drugs* [read "therapeutic medications"] *in horse racing are:*
>
> *(1)To ensure fair competition*
> *(2)To protect the welfare of horses*
> *(3)To protect the breed from becoming debased*

The EHSLC booklet also notes that:

"The rules of racing are not intended to discourage the proper veterinary care of racehorses if such treatment would not threaten any of these important objectives. Furthermore, modern forensic analysis can sometimes detect drugs (including metabolites) long after administration and, as such, can make it difficult for veterinary surgeons to give advice about how soon after treatment a horse may be raced."

Clearly, if horses are not to be deprived of proper veterinary care, then suitable information on the time-after-administration that therapeutic agents or their metabolites may be detected in racing horses must be made available to the veterinary profession.

Continuing this line of thought, the American Association of Equine Practitioners (AAEP), in its 2000 Policy on Therapeutic Medications in Racehorses, stipulates that:

> *"detection of pharmacologically-insignificant levels of therapeutic medications should not constitute a violation of medication rules".*

While easily identified, the problem of equine medication control has not been easy to approach. Proposed solutions have taken a number of different forms, many of which are presented below. It should be noted that the fact there are numerous different approaches to this problem immediately establishes that none of these individual solutions is yet perceived as sufficiently satisfactory to have prevailed.

1) The "Thresholds"–"Limits"–"Decision Levels"–"Reporting Levels" Approach

These descriptors generally identify specified "*quantitative limits*" in serum or urine. The advantage of published "*limits*" is that they are, by definition, standardized, transferable and applicable worldwide. Beyond this, research data and results are generally presented in quantitative form and can be readily interpreted and applied in terms of "*quantitative limits*." Quantitation is, in fact, the language of science.

A major advantage of the "threshold" approach is that adoption of a "threshold" immediately standardizes testing for that agent in all jurisdictions adhering to that threshold.

The disadvantage of the "*thresholds*" approach is that threshold information, "5 µg/ml in plasma," for example, is not directly useful to horsemen. Thresholds, therefore, need to be translated into recommended "*withdrawal time guidelines*" that can be readily utilized by horsemen.

2) The "Detection Time" Approach

The historical approach to this problem has been to develop tables of "*detection times*," or times post-administration during which particular agents can be detected. At least three formal official published sets of "*detection time*" data, from Canada, Australia

and the European group (EHSLC) are available, and these tables are summarized in later sections.

The problem with "*detection times*" is that they are method- or laboratory-specific, and are each, therefore, local solutions to the problem. Additionally, "*detection times*" are developed in small numbers of horses, and the veterinary practitioner must use this information as a guideline when he develops the "*withdrawal time guideline*" advice that he presents to his clients.

3) The "Official Withdrawal Time" Approach

At least one racing jurisdiction explicitly expresses its medication rules in terms of the number of days before post that a certain medication should not be administered. In this approach, the regulators apparently assume the responsibility of translating the analytical data generated in their laboratories into specific "time of administration" information.

4) Suggested "Withdrawal Times" Approach

The Texas Racing Commission "Medication Information" booklet lists a total of 60 ARCI classified medications with "suggested withdrawal times" for each. Medications listed in the Texas Racing Commission "Medication Information" booklet that are not ARCI classified have not been included in this overview.

5) The so-called "Zero Tolerance" Approach

Some jurisdictions maintain that they have a "zero tolerance" policy for certain drugs, taking the position that no amount whatsoever of these drug(s) are permitted in horses in their jurisdiction. Such claims, however, are misleading, because chemists cannot quantify down to zero. Racing chemists can quantify only down to about 1 quadrillion molecules (1,000,000,000,000,000, or 10^{15}), more or less, in a horse. Professional chemists never certify that a sample contains zero drug; all they can report is that no drug was detected, and then state the "limit of detection" of the method.

Under a "zero tolerance" policy, a jurisdiction must, in good faith, apply the most sensitive detection technology possible. For most illegal medications, this is not a problem. But problems can arise when this policy results in the detection of irrelevant traces, occurring as environmental contaminants, of politically sensitive substances.

Morphine is a typical politically sensitive substance. The problem in this case is that a trace (one quadrillion, 10^{15} molecules) is, for morphine, more or less one thousand fold less than the number of molecules required for pharmacological effect. In a horse, 5 mg of morphine is an ineffective dose, but it is about 10^{19} molecules. Data from our group suggest that this dose will produce a peak morphine (plus metabolites) concentration in equine urine of about 1,000 ng/ml (ppb) (see reference #26). However,

5 ng/ml (5 ppb) of morphine can be readily detected by ELISA and confirmed by mass spectrometry.

It is, however, not unusual to find traces of morphine (plus metabolites) in equine urine of about 50-100 ng/ml (ppb), with little indication of the source. Reported sources of morphine in horse urine are poppyseeds from human foodstuffs (California), bakery waste contamination of foodstuffs, wild poppies contaminating equine foodstuffs (Australia), and, in Europe, contamination of hay dried in a commerical dryer following the drying of opium poppies grown under license.

In this regard, recent research at the Horse Racing Forensic Laboratory in England has shown that orally-administered poppyseeds can yield equine urinary concentrations of 110 ng/ml (ppb) of morphine (plus metabolites, by mass spectrometry) (Ginn et al; see reference #25).

These considerations are likely the reasons that the Louisiana and Ohio authorities have recently established urinary "limits" or "cut-offs" for morphine (plus metabolites, by mass spectrometry) of 75 parts per billion, and 50 parts per billion, respectively (see page 15, item 34).

These limits are very conservative when compared with the limits in place in human forensic testing. United States Substance Abuse and Mental Health Services Administration (SAMHSA) guidelines allow for detection of up to 2,000 ng/ml (ppb) of morphine in human urine before regulatory action is taken (see table below and reference #24). This "cut-off", forty-fold higher than the State of Ohio's horseracing "limit" or "cut-off", was established to distinguish between concentrations due to innocent sources of morphine in human urine and concentrations associated with abuse of this agent.

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

Marijuana metabolite[1]	15 ng/ml	urine	SAMHSA	23
Cocaine metabolite[2]	150 ng/ml	urine	SAMHSA	23
Morphine	2,000 ng/ml	urine	SAMHSA	24
Codeine	2,000 ng/ml	urine	SAMHSA	24
6-Acetylmorphine[4]	10 ng/ml	urine	SAMHSA	24
Phencyclidine	25 ng/ml	urine	SAMHSA	23
Amphetamine	500 ng/ml	urine	SAMHSA	23
Methamphetamine[3]	500 ng/ml	urine	SAMHSA	23

1: Delta-9-tetrahydrocannabinol-9-carboxylic acid
2: Benzoylecgonine
3: Specimen must also contain amphetamine at a concentration > 200 ng/ml
4: Test for 6-AM when the morphine concentration exceeds 2,000 ng/ml

6) Unofficial or "Practitioners' Withdrawal Times"

In this approach, veterinarians, horsemen or other interested parties pool their historical information on the sensitivity of testing in a certain jurisdiction. In essence, horsemen learn by trial and error when to cease medicating horses prior to post, and then organize their findings into printed tables of unofficial "*withdrawal times*." The English data presented in Table 6 represent such a table of Unofficial "Practitioners Withdrawal Times," as is the AAEP data from a number of American racing jurisdictions.

7) Published "Performance Specifications"

The Association of Official Racing Chemists (AORC) and the International Federation of Horseracing Authorities (IFHA) have developed a set of performance specifications that reflect ***"a reasonable level of capability, practicable and foremost a credit to the laboratories under the Federations umbrella, but not deliberately set to the lowest common denominator achievable by all. It is expected that most of the laboratories under the Federation's umbrella would be able to demonstrate that they can find them and prove their presence reliably."***

4) Definitions

1) "Threshold"

A "*threshold*", or "*limit*", or "*cut-off*", or "*decision level*", or "*reporting level*" is any defined drug or drug metabolite concentration in a biological fluid that determines whether regulation should take place or not. In racing, concentrations greater than the stipulated "*threshold*" initiate regulatory action, while concentrations below the "*threshold*" are of no regulatory interest. The terms "*limit*", "*threshold*", "*cut-off*", "*decision level*", "*reporting level*", and "*limitation*" regarding the sensitivity of testing are equivalent in scientific and regulatory terms. In this review the terms "*threshold*" or "*limit*" will be used interchangeably as the standard descriptors for this concept.

2) "Detection Time"

A "*detection time*" is an officially- or scientifically-reported period of time after drug administration during which the drug, or medication, or a metabolite thereof has been detected in the blood, urine or other body fluid of a horse.

"*Detection times*" are almost always based on results obtained in experimental situations with small numbers of horses that are not actually racing. These limitations must be kept in mind when extrapolating from reported "*detection times*" to actual "*withdrawal times*."

The "*detection times*" presented in Table 2 are from official publications of racing authorities or closely related groups. We have not attempted to evaluate the scientific literature because of the difficulty, if not impossibility, of relating individual scientific experiments to these published "*detection times.*" The scientific literature, however, can be an important source of information and a helpful guide with regard to "*detection times*."

3) "Withdrawal Time"

A "*withdrawal time*" is a suggested period before an event to cease administration of a medication to minimize the risk of post-race detection of a residue of the medication. When establishing a "*withdrawal time*", veterinarians must take numerous factors into account, including but not restricted to, the longest known "*detection time*" for the drug, the dose used, the form in which the drug was administered, the route of administration, the duration of treatment, the sensitivity of testing/known detection time, the chemical and pharmacokinetic characteristics of the agent, the appropriate level of risk, and any unique characteristics of the horse or the event in which the horse is participating.

"*Withdrawal time*" estimates are almost always significantly longer than the longest reported "*detection time*" for an agent and **can vary from jurisdiction to jurisdiction depending on the testing methodology** employed by the laboratory.

"*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.

Based on the above considerations, it is clear that any "*withdrawal time*" recommendation carries with it a finite possibility of error. The likelihood of an inadvertent error occurring (a residue being detected) increases with the number of animals to which a given "*withdrawal time*" is applied.

One of the larger numbers of animals to which a "*withdrawal time*" might be applied would be the number of horses racing in an entire jurisdiction. Given the greatly increased probability of a residue being detected when the number of animals is very large, such applications of the "withdrawal time" concept are unlikely to be satisfactory.

4) "Zero Tolerance"

"*Zero tolerance*" is a myth; no chemist can detect down to zero. Therefore, a chemist cannot declare a sample "negative"; all a chemist can say is that the substance was <u>not detected</u>, and specify the Limit Of Detection [LOD] of his method.

In effect, "*zero tolerance*" means that the most sensitive method possible is utilized. The limit, or tolerance, therefore, is determined by the technology applied, and is called the SENSITIVITY OF THE METHOD.

Application of this approach, therefore, results in steadily increasing sensitivity of testing.

5) Screening Test

A *screening test* is a pre-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 ELISA tests are classic examples of *screening tests*. By definition, a *screening test* yields a "presumptive" identification, which may or may not be correct.

6) Confirmatory Test

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* is extremely good evidence for the presence of the reported substance.

7) Qualitative Test

A *qualitative test* is a test that simply identifies the presence of a prohibited substance in a test sample.

8) Quantitative Test

A *quantitative test* is a test that both unequivocally identifies and establishes the concentration of the prohibited substance in the test sample.

9) Analytical Standards

An *analytical standard* is a certified chemically pure sample of a drug or drug metabolite used by an analyst as a reference in order to reliably and reproducibly identify and quantify drugs and drug metabolites.

10) Validated Method

A *validated method* is a qualitative or quantitative analytical method that has been rigorously characterized and tested, in more than one laboratory, so that it reliably performs as described in the Standard Operating Procedure (SOP).

11) Standard Operating Procedure (SOP)

A *Standard Operating Procedure (SOP)* is a complete description of an analytical method or procedure, which enables its confident replication in the hands of an appropriately trained and equipped individual.

5) Factors Affecting "Withdrawal Times"

It is important to allow an adequate "*withdrawal time*" between the use of a therapeutic agent and competition. Unfortunately, "*withdrawal time*" guidelines are affected by a large number of poorly characterized or understood factors. Any guideline, therefore, cannot be inclusive of all the possible variations that can affect a "withdrawal time" in any individual horse.

The following, in the authors' best estimate of order of importance, is a list of factors influencing "*withdrawal times*."

1. **Dose:**
   Drugs administered at *gram* doses (2-10 g/horse) are much more likely to be detectable for
   longer periods than drugs administered at low *milligram* doses (5 mg or less/horse).

   Precaution:
   Know the quantity of the drugs/medications you administer in *milligrams*, not in milliliters.

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 for a drug exists or has just been introduced, a rule of thumb is to at least double
   the "*withdrawal time*" that was used prior to development of the ELISA test.

3. **Local testing procedures:**
   Testing methods are not standardized, so what constitutes a violation in one jurisdiction may not necessarily constitute a violation in another. For example, in Canada certain "*detection times*" are shorter than the "*detection times*" for the same agents in the United States.

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

4. **pH of the urine:**

The pH of the urine that the horse produces post-race can be a major factor in determining urinary drug or drug metabolite concentrations, and therefore the "*withdrawal time*." While this factor is outside the control of the horseman, it may play an important role in determining the "*withdrawal time*" and or the significance of a urinary drug finding.

5. **Route of administration:**

Oral administration can greatly prolong "*withdrawal times*." It can take up to five days for pills or tablets to pass through the intestinal tract of a horse, so a pill or tablet that breaks down slowly in the intestinal tract can theoretically release drug into a horse's system for five days.

Precaution:
Any therapeutic medication that must be administered 24 to 48 hours before an event should be administered intravenously.

6. **Frequency of drug use:**

Repeated or long-term administrations with some drugs, especially repeated oral administrations, can greatly extend "*withdrawal times*." Good examples of such agents include isoxsuprine and the acepromazine family of tranquilizers.

Precaution:
Where possible, avoid repeated administrations.

7. **Contamination of the horse's environment:**

Any stall that a horse inhabits during a course of therapy becomes contaminated with the agent in question. This has been shown to occur even if the drug is administered parenterally.

Precaution:
Care should be taken with orally-administered agents to ensure that the stall does not become contaminated or that other horses in the stable do not become exposed to the medication. Move a treated horse to a fresh stall during the "*washout*" period prior to competition to eliminate the possibility of environmental contamination extending the "*withdrawal time*."

8. **Time of last meal:**

If drugs 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.

9. **Release times of the drug preparation:**

Preparations for either oral or intramuscular use are formulated in such a way that will likely extend "*withdrawal times*." The same is true for sustained-release preparations, which are specifically formulated to delay release of the drug.

Precaution:
Where possible, avoid sustained-release preparations.

10. <u>Drug formulation:</u>

For any dosage form other than simple intravenous (IV) administration, differences in the formulation of a medication may result in substantially different "*withdrawal times*." These differences can be marked for oral formulations.

Precaution:
Never assume that seemingly similar products from different manufacturers will have the same "*withdrawal times*."

11. <u>Other factors:</u>

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

For more detailed information, consult your veterinarian and the appropriate regulatory body for your particular sport and jurisdiction. See also *Equine Drugs and Vaccines: A Guide for Owners and Trainers* by Eleanor M. Kellon, V.M.D. (Breakthrough Publications, 1995) and *Drugs and the Performance Horse* by Thomas Tobin (Springfield, IL: Charles C. Thomas, 1981) or relevant publications that may be available in the scientific literature.