Uniform Medication Rules:

Where are we now?

CLARA FENGER, DVM, PHD, DACVIM

"Uniform" Medication Rules:

- Regulators, horsemen and veterinarians alike were in agreement that Uniform Medication Rules across all jurisdictions would simplify compliance with the rules:
 - Permit the use of therapeutic medications for the treatment of a living breathing animal athlete using the most advanced Modern Medicine for the benefit of the horse
 - Prohibit the use of all performance enhancing drugs (PEDs) within proximity to racing for a level playing field
 - Impose penalties sufficiently harsh to discourage cheating

What Happened?

A. Commonsense, logical approach to how long a substance should be withdrawn from a horse before racing (eg 24 hours on a NSAID, or a week on a joint injection)

B Science Happens

C: Thresholds in blood or urine & withdrawal guidelines



The Racing Medication and Testing Consortium (RMTC) was charged with funding and interpreting relevant research to determine thresholds and withdrawal guidelines: "95/95 Tolerance" (Risk of positive = 1:20)



Why??? Rampant Cheating???

- The rollout of the Uniform Medication Rules resulted in record positives in many jurisdictions, and a deafening silence in others
 - That much difference between the amount of nefarious activity in different jurisdictions?
 - Veterinarians and horsemen couldn't understand the new withdrawal guidelines, even though some of the affected states shared horses and horsemen with unaffected states?
 - ► Or something else.....?

Let's look inside the black box

Could it be the "Science"?



- Premise: No NSAIDS within 24 hours. Determine a threshold for a 24 hour withdrawal
- Study done (Stanley et al, 2006), supported a 50 ng/mL threshold
- RMTC still proposed a 20 ng/mL threshold



- Premise: No NSAIDS within 24 hours. Determine a threshold for a 24 hour withdrawal
- Study done (Stanley et al, 2006), supported a 50 ng/mL threshold
- RMTC still proposed a 20 ng/mL threshold



- Premise: No NSAIDS within 24 hours. Determine a threshold for a 24 hour withdrawal
- Study done (Stanley et al, 2006), supported a 50 ng/mL threshold
- RMTC still proposed a 20 ng/mL threshold



- Premise: No NSAIDS within 24 hours. Determine a threshold for a 24 hour withdrawal
- Study done (Stanley et al, 2006), supported a 50 ng/mL threshold
- RMTC still proposed a 20 ng/mL threshold



- Premise: No NSAIDS within 24 hours. Determine a threshold for a 24 hour withdrawal
- Study done (Stanley et al, 2006), supported a 50 ng/mL threshold
- RMTC still proposed a 20 ng/mL threshold



Soooo...Research supports a 50 ng/mL threshold

RMTC still proposed a 20 ng/mL threshold

Intentional setup of the horsemen?RMTC didn't read the research?

Of the 26 permitted therapeutic medications, only 7 are based on published research

Controlled Therapeutic Medication	Threshold	Withdrawal Guideline	Dosing Specifications	Reference Notes	Note
Acepromazine	10 nanograms per milliliter as 2-(1- hydroxyethyl) promazine sulfoxide (HEPS) in urine	48 hours	Single intravenous dose of acepromazine at 0.05 milligram per kilogram	University of California at Davis project	applicable analyte is metabolite HEPS
Albuterol	1 nanogram per milliliter of urine	72 hours	720 micrograms total dose intra- nasal only ¹ . Based upon dosing up to 4 times per day	European Horseracing Scientific Liaison Committee Data	See Endnote
Betamethasone	10 picograms per milliliter of plasma or serum	7 <mark>da</mark> ys	Intra-articular administration of 9 milligrams of Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, USP (American Regent product #0517-0720-01) ²	RMTC study	Intra-articular dosing only - applicable analyte is betamethasone in plasma or serum

3 of the 26 medications have NO listed justification for the levels at all:

Omeprazole	l nanogram per milliliter of urine	24 hours	Single oral dose of omeprazole as Gastrogard® at 3.9 milligram per kilogram	Applicable analyte is omeprazole sulfide in urine
Prednisolone	1 nanogram per milliliter of serum or plasma	48 hours	l milligram per <mark>k</mark> ilogram orally	Applicable analyte is prednisolone in plasma or serum
Xylazine	0.01 nanogram per milliliter of plasma or serum	48 hours	Intravenous	Applicable analyte is xylazine.

Of the 7 therapeutic medications supported by research, 4 do not use appropriate doses

Dantrolene	100 picograms per milliliter of 5-hydroxydantrolene in plasma or serum	48 hours	Oral administration of 500 milligrams of dantrolene as paste (compounding pharmacy) or capsule formulation (Proctor and Gamble)	Journal of Veterinary Pharmacology and Therapeutics 34, 238– 246		¹ ∕₂ dose
Detomidine	1 nanogram per milliliter of carboxydetomidine in urine; Level of Detection for detomidine in plasma	72 hours	Single sublingual dose detomidine (Domosedan [®] gel at 40 micrograms per kilogram)	The Veterinary Journal, 2012 Oct. 10 http://dx.doi.org/10.101 6/j.tvj1.2012.08.016		Sublingual
Mepivacaine	10 nanograms total hydroxymepivacaine per milliliter of urine or above Level of Detection of mepivacaine in plasma	72 hours	Single 0.07 milligrams per kilogram subcutaneous dose of mepivacaine	European Horseracing Scientific Liaison Committee data		1.5 mL
Methocarbamol	1 nanogram per milliliter of plasma or serum	48 hours	Single intravenous dose of 1. milligrams per kilogram methocarbamol as Robaxin [®] or 5 grams orally	Journal of Veterinary Pharmacology and Therapeutics doi: 10.1111/jvp.12068	Applicable analyte is methocarbamol in plasma or serum	Single dos

Of the 7 based on published research, research on 3 substances supports a different threshold than the 1 suggested by the RMTC

Methylprednisolone	100 picograms per milliliter of plasma or serum	7 days	Total dose of methylprednisolone acetate suspension in one articular space. ³ The recommended withdrawal for methylprednisolone acetate is a minimum of 21 days at a 100 milligram dose	Journal of Veterinary Pharmacology and Therapeutics volume 37, Issue 2, pages 125–132, April 2014	Applicable analyte is methylprednisolone	????
Flunixin	20 nanogram per milliliter of plasma or serum	32 hours	Single intravenous dose of flunixin as Banamine® (flunixin meglumine) at 1.1 milligram per kilogram	University of California at Davis/RMTC study	Secondary anti- stacking threshold: 3.0 nanograms per milliliter of plasma or serum (Administration 48 hours prior)	50 ng/r
Phenylbutazone	2 micrograms per milliliter of plasma or serum	24 hours	Single intravenous dose of phenylbutazone at 4.0 milligrams per kilogram	ARCI model rule	Secondary anti- stacking threshold: 0.3 micrograms per milliliter of plasma or serum (Administration 48-hours prior)	2.5 ug/

Penalties for Stacking NSAIDS are severe **CONCLUSIONS:** It was concluded that the combination of PBZ+FM was not more effective than either PBZ or FM alone. These data do not support the hypothesis that the combination is more efficacious at these dosages than either drug alone in this model of acute foot pain

9 substances are regulated in picogram quantities

Substances are for intra-articular injection, and represent doses or uses that deviate from Standard of Practice

3 have pg levels in urine and limit of detection (potentially moving target) in serum/plasma

"Limit of Detection" no longer represents common sense regulation for any substances:





Example: Other therapeutic medications
In most cases, picogram detection does not represent common sense regulation for substances:

In Urine, the Federal Government considers levels below 150 ng (1000 X more than a picogram) for cocaine metabolites as likely to result from **environmental** contamination (like handling money)

Substance	(institut drug text level (institute away) (rig/ml.)	Confirmatory dra test level (OC-MS (ng/ml.)
Marijuana metabolitorh	50	15
Cocsine metabolites*	300	150
Oriate metabolitus	2000	2000
Phenoyolistane	25	25
Amphetamines	1000	500
Methamphetamine"	Incomplete data	500

Data from reference 5.

"Limit of Detection" no longer represents common sense regulation for any substances:



Example: Cobalt

Cobalt is a necessary trace mineral, required at a rate of 0.5 to 1.1 mg in the horse's daily diet All complete feeds and most vitamin/mineral supplements contain supplemental cobalt Most vitamin preparations for "jugs" contain small amounts of cobalt.



Example: Cobalt

Recently, cobalt has made the headlines, and several jurisdictions have established thresholds....IN THE COMPLETE ABSENCE OF SUPPORTING DATA

When a large population of horses is surveyed, cobalt levels cluster around a very low number, with a tiny percentage of "high testers"



Example: Cobalt

Almost every study completed on this substance has thrown out "outliers"

- Preliminary data from USTA funded research supports a threshold of 70 ppb
- The scientific literature supports a threshold of





Time to start thinking OUTSIDE the box...

Or at least take a good hard look at what's going on in there.