At The Threshold

Moderator:
Dr. Rick Arthur, Equine Medical Director, California Horse Racing Board

Speakers:
Dr. Heather Knych, Specialist of Equine Pharmacology, University of California, Davis
Dr. Robert Lewis, President, Elgin Veterinary Hospital, Inc.
Dr. Richard Sams, Professor and Program Director, Racing Laboratory, University of Florida

Mr. Steve Barham: For the last — last day of the symposium, I’d like to thank the breakfast sponsor, Equibase; the panel sponsor, International Sound; and for the break that sponsor is going to be Delaware North. Also, I’d like to remind everybody, out in the foyer from 9:30 until 11:00, we’re going to have some student projects. They’re listed in your program. Please stop by, talk to the students and look at what they’ve done. Some of those projects are actually pretty interesting, and we’re proud of the students that have done it. I’m going to turn it over to Dan Fick just for a short announcement before I introduce the moderator of the panel. Dan?

Mr. Dan Fick: Thanks Steve. Some of you may know but the alumni of the Race Track Industry Program have formed an association over the last year. We finally decided it was time to formalize the fact that we work together on a lot of things within the industry. Our primary focus is going to be promoting the program and more importantly promoting the students; both helping them get jobs within the industry or internships; but also in these tough times helping them with some scholarship funds.

Just wanted to reach out to all of you for three reasons. One, if you’d like to get involved with us and help with our scholarship fund, which is going to be a memorial scholarship fund to remember a few of the alumni that are no longer with us. It’s also going to be an opportunity, if there are some alumni in the audience, and I see a couple of you, to join up. Then if you would just like to be involved with this program and these students, maybe help us sponsor an event or host an
event at your race track, let us know. I left a green bag up front. If you’d like to get involved, just drop your card in, and we’ll get in contact with you. Or you can contact me at dfick@jockeyclub.com. If you feel moved to make a contribution to the scholarship fund, you can stick that in the bag too. Thank you.

Mr. Barham: Okay. Most people probably know Dr. Arthur, who is the moderator of this panel. It seems like we usually always call on him to moderate panels like this because of the breadth and depth of knowledge he has, and he can also seem to keep people in line. With that, I’ll turn it over to him and —

Dr. Rick Arthur: Thank you very much. The title of this talk is “At the Threshold”. I will tell you we could spend all morning on this from a technical perspective, and it would become probably a rather in-depth discussion of the issues. We’re just going to try to just introduce some concepts. We’re going to have a few short presentations and open this up to Q & A so that we can hopefully get on the same page. Could you go ahead and run the video?

While I’m giving the rest of this introduction, I want you to watch the BC Marathon. It’s probably as interesting as you’re going to see. It’s a good example of how difficult some of these drug issues can be. The speakers are going to be Dr. Heather Knych, who is the equine veterinary pharmacologist at the Maddy Laboratory. She’s going to be talking a little bit about how to do PK and PD studies; that’s pharmacokinetic and pharmacodynamics. Dr. Rick Sams about what the RMTC is doing in terms of developing withdrawal times and the statistics that go into that and Dr. Bobby Lewis who’s chairman of the RMTC and a highly respected equine surgeon and a past president of the AAEP.

We often hear the phrase “zero tolerance” bandied about. The fact of the matter is there’s no such thing. In every country, in every jurisdiction for every drug there’s threshold levels. Sometimes those are technologically driven. Sometimes they’re deliberately chosen. Dr. Tobin’s thrown out a concept of “no effect” thresholds some time ago. Intellectually I agree with the concept, but in practicality it becomes very, very difficult to do. Trying to figure out what affects a race and what doesn’t is very, very difficult.

When you see the end of this race, now I want you to consider if you were the second finisher in this race; and the winner tested positive for let’s say two drugs that have been in the press on very high profile cases. If the winner tested positive for lidocaine or ipratropium at any level at all, and you were the second place finisher, or you bet on the second place finisher whether you would be convinced that there was no pharmacological effect.

The fact of the matter is no one would know. The fact is that drugs are given to have an effect. That’s the only reason they’re used. What difference would it make in the outcome of this particular race?

There was a study funded by the HBPA at the very beginning on clenbuterol. It was done at a university and it was done with a treadmill. The author concluded that
clenbuterol doesn’t affect performance. The fact of the matter is that the sensitivity in his laboratory tests was only five percent. In reality he would not have been able to differentiate the performance of Secretariat in the Belmont and the horse that ran second to him. That doesn’t make any sense. I looked at the charts from Hollywood Park yesterday, and the fact of the matter, every race would have been changed in outcome if a horse in there would have changed their performance by one-fifth of a second in the time of the race.

The fact is that it’s very, very difficult to say that drugs don’t affect performance. Look at this finish out of a mile and three-quarter. How can you say that a drug doesn’t make a difference? The Melbourne Cup had a very similar outcome this year, year before at a mile and a half race that was separated by a nose. These are very, very difficult issues to address. Thresholds are set as either deliberately or in the laboratory. All drugs have thresholds. We just try to do the best we can, and hopefully you’ll get an idea how difficult that is to do.

Why don’t we start off with Dr. Knych, and she’ll talk about some of the pharmacokinetic and pharmacodynamic research she’s done at UC Davis Maddy Lab.

**Dr. Heather Knych:** All right. Well thank you very much. Today I’m going to talk a little bit about pharmacokinetic and pharmacodynamic studies; and how we go about setting these studies up and some of the limitations; and considerations that we need to think about when designing the studies. Time permitting; I have essentially a real world example of one of the drugs that we’ve been looking at most recently to illuminate both the pharmacokinetic and pharmacodynamic effects.

For those of you who aren’t familiar with these two concepts, I just want to take a second to define what exactly pharmacokinetics is and pharmacodynamics is. Kinetics is just simply what the body does to a drug, so it’s a study of the movement of a compound in the body. We administer a drug, and we need to have that drug absorbed from the site of administration. If we give something orally, it needs to be absorbed either from the stomach or the GI tract. Then it’s distributed by the blood to different tissues where it’s actually having its effect. Pharmacokinetics also describes excretion or elimination of the drug from the body, so both metabolism and excretion.

Pharmacodynamics on the other hand is just essentially what the chemical does to the body. It’s some kind of physiological or pharmacologic effect. For instance an increase in heart rate, decrease in heart rate, sedation, Central Nervous System (CNS) stimulation or any kind of measurable physiologic effect. I just have this little — sorry about that — this schematic right here which shows how these two concepts interrelate. This top part is pharmacokinetics, the bottom part being pharmacodynamics.

Here’s our drug being administered. We have absorption, distribution and elimination. All of which determine the ultimate concentration of the drug at the
site of action, and then that's manifested as some kind of pharmacologic effect; so some kind of toxic effect or some kind of efficacious effect.

These pharmacokinetics, pharmacodynamics studies become more important especially as we develop more sensitive analytical instrumentation, so we can detect such low levels of drug now that the question arises as to whether these low levels actually have some kind of physiologic effect and whether this can affect the performance of a horse and ultimately the outcome of a race.

I just want to introduce the concept of a blood concentration versus time curve, so this is what we have here. On this Y axis we have a concentration of a drug. In this case, the example I have up here is penobarbital. On this X axis is time. This simply shows how the drug decreases as a function of time. We can overlay this — overlay this graph with these pharmacodynamic effects. You can see at high levels of drug, we have the effect of unconsciousness.

As the drug concentrations decline we have this return of this palpebral response, a riding reflex and ultimately the animal is awake. Drug concentrations decrease over time, and we run the full gamut of pharmacodynamic effects. Alright so pharmacodynamics is just — essentially produces an effect.

This is very much a simplified version of how we set up our drug administration studies. We have our drug. We administer it to our horse. We collect samples, either blood, urine or whatever we want to look at. In our lab, we use mainly mass spectrometry to measure the plasma concentrations of a drug over time. Then we can plot that on a graph here, which is a plasma concentration versus time curve, so essentially what you saw on the last slide. What I don’t have up here is that we can also measure the pharmacodynamic effects at these different time points, correlate that back to plasma drug concentrations and overlay them much like we did on the previous example.

When we set these studies up there’s a number of different considerations that we need to take into account, and it’s not quite as simple as I portrayed it on the previous slide. First of all for our study horses, we try ideally to have a representative population of animals. For these elite athletes, these very fit race horses, the closest that we can usually come is to have what we like to call an exercised research herd. These animals are fit and exercised. However, in reality, at least at UC Davis, what we generally end up with is something more along these lines, which is what we call a sedentary research horse. That’s just simply because it’s so expensive to keep these horses, to keep them exercised. We need a lot of trained personnel to keep the horses fit, so we have to default to our sedentary horse.

Ideally we would want this exercised horse. There’s been a number of studies that have shown that there are differences in drug clearance between fit versus exercised horses, so we try to get as representative as possible but obviously there are limitations with that.
Another important factor is the actual number of animals. The generally accepted statistically significant number of animals is six. However, we are looking, especially when we get into really subtle differences in pharmacodynamics, it’s nicer to have a larger population and a larger number of horses so that we can detect and have the statistical power to detect these really subtle differences.

Another thing to take into account when we set up these studies is the drug administration, so the dose. We want to try to replicate what’s happening, for instance, on the track as closely as possible. We need to administer a very similar dose, know what route of administration. For something like an oral drug, it’s nice to know whether this drug is administered in the feed, whether it’s administered via dosing syringe just so we can kind of replicate dosing conditions as closely as possible.

Another important factor is fasting. Are the animals given the drug when they’ve been fasted, which can significantly affect absorption. We then, in these drug administration studies, collect our samples, analyze them. As I mentioned previously we tend to use mass spectrometry. Then we can do pharmacokinetic analysis and pharmacodynamic analysis and correlate those two.

I put this picture up here because I think it is a nice — it kind of shows or emphasizes just how many samples we generate during one of these studies. This is a picture from one pharmacokinetic study that we did about a year and a half ago. There were 12 horses. There’s about 20 boxes here, and each of these boxes hold about 80 samples. It’s a tremendous number of samples that have to be analyzed. It’s a tremendous amount of technician time. Reagents to analyze these samples can get quite costly and just takes a lot of time.

Another factor that we need to look at, or another thing that we need to take into consideration, is the selection of our pharmacodynamic model, so what do we want to look at? It’s largely driven by the particular drug that we’re looking at. Is this something that’s supposed to alleviate pain for instance? Is this a sedative? Is this a CNS stimulant? It could be as simple as measuring heart rate, so we can take a stethoscope and listen to the heart. We can also hook up an ECG to continuously monitor heart rate as well as to look at rhythm. We can collect extra samples, measure blood glucose or total protein.

Then we can get into a little more complicated models. This next — this list that I have right here pertains more to lameness. Pain manifested as lameness, so we can measure stride lengths. Presumably when you give an analgesic agent, and the animal doesn’t feel quite as much pain, the stride length might increase. We can look at the circumference of an inflamed joint, circumference increases with inflammation. We can measure flexion. We can also do force played analysis studies.

These can get more and more complicated. There are a number of other pain models for measuring colic. We can just look at a lot of different things. We can also measure sedation or excitation. One of the most commonly measured
parameters is a chin to floor distance with sedation. As the animal becomes more sedate, their head drops and their chin actually becomes closer to the ground. We can measure that distance and compare that back to baseline or what that distance was prior to administration of a drug.

Okay. Since I think I still have a little bit of time, I’m just going to give an example of one drug that we’ve looked at most recently. That drug is yohimbine, and the reason we did a study with this is we had one positive urine sample. This is from a standardbred that was racing in California. We weren’t really sure whether this was residual from some veterinary procedure, or whether this was some attempt at helping enhancing the horses performance. Yohimbine is a reversal agent. It reverses the actions, the sedative actions of xylozene. There have been some anecdotal reports that yohimbine causes CNS excitation. Whether that was the point of the administration we don’t know and we probably never will know.

Our goal was to kind of look at the pharmacokinetics and measure some of the pharmacodynamics just to kind of get a better idea. The way we set our study up was we used eight horses and, unfortunately, we don’t have an exercised research herd, so we had to default to our sedentary research horses. We had seven thoroughbreds and one standardbred. The dose we used was .12 milligrams per kilogram intravenously, and we collected blood samples at a number of different time points; both before and post drug administration. All of these samples were analyzed using liquid chromatography – mass spectrometry (LCMS) and then we did pharmacokinetic analysis.

I put this graph up here because this is what was in the literature prior to us performing our studies. We tried to find out what pharmacokinetic studies had been done in the horse and essentially this was the only one. The study was performed with just four horses so a very small sample size. They collected samples out to about three hours, and at that point they were still detecting drug concentrations. We wanted to do our study and try to get a more complete pharmacokinetic profile and also look at the pharmacodynamic effects. We had the advantage of having their data so we knew we had to go out further than three hours. We also had the advantage of having easy access to a mass spectrometer where we could continuously measure samples and make sure it had been cleared before terminating our study.

These are just — these are the results from the pharmacokinetic portion of the study. This up here is the plasma concentration versus time curve. We had drug measurable out until about 12 hours. Down here is the individual pharmacokinetics of all the horses with the mean being over here in this column. I’m not going to go through all of these numbers. I just simply want to point out there is variation in the horses. We did use eight horses but this variation just emphasizes that it’s nicer when you have a larger sample size or a larger number of horses to actually assess pharmacokinetics or pharmacodynamics.

We measured a number of different pharmacodynamic parameters, and I’m just going to show you a few here. This is what I was talking about previously with the
chin to floor distance. You can measure — I apologize I don’t have the pre-drug administration picture here. It’s kind of obvious the horse’s head is beginning to drop. Has this wide stance as he tries to remain upright I guess. This graph right here is the average distance from chin to floor for all of our horses over time. Here’s our baseline. This red arrow — I apologize for not labeling it, but this is where the yohimbine was administered. We had a slight decrease in chin to floor distance and then it kind of evens out.

You can also see that there is a wide variation as is represented by these huge arrow bars. We had two horses that were quite obviously sedate, but we had a number of horses that didn’t appear to respond. Once again, it just shows the wide variation. Perhaps if we had a larger sample size, maybe this was very subtle change, but maybe it would have been a statistically significant response.

We also looked at heart rate and rhythm. We hooked up an ECG, and we took continual measurements of the rate and rhythm. The ECG I have over here is prior to administration; this being after. You can just see by looking at these peaks that we had an increase in heart rate with administration of this drug. This only lasted a short period of time and then returned to normal. We measured pack cell volume (PCV) as well, and you can see right after administration of the drug we did have an increase in PCV, and this was a significant increase but it fell off after about 30 minutes or so.

I’m not going to go through this one. This was just another example of a drug, but in the interest of time. Basically the points I want you to go home with are that there are very few, and I didn’t actually talk too much about this, but there are very few PK PD studies in the horse. If you look in the literature, they just don’t exist. With the advent of all these new technologies, we can detect extremely low plasma concentrations. The question becomes, are these concentrations physiologically relevant? Are they causing any effect on the horse that could possibly enhance performance and ultimately influence the outcome of a race?

Lastly, it’s very difficult and it’s extremely expensive to conduct and design and then ultimately interpret the findings from the PK PD studies. Then the question again, are these representative? Sorry. I have a bunch of things at the end here.

Dr. Arthur: Thank you Heather. Our next speaker is Dr. Rick Sams who is director of the racing laboratory at the University of Florida and a professor of pharmacology. Thank you Rick.

Dr. Richard Sams: I want to thank the organizers of this panel discussion for inviting me to make a presentation this morning on drug withdrawal and threshold studies that we’ve been involved in at the University of Florida. Studies that originally were supported by the Florida Division of Pari-Mutuel Wagering, the Florida HBPA and more recently with funding from the Racing Medication and Testing Consortium, Merial and a number of other agencies and organizations.
As Heather and others have pointed out, the advent of new analytical methodology makes it possible now to detect drugs and other related substances at concentrations that weren’t possible just a few years ago. Modern LCMS methods have lowered detection limits for many analytes well below those that are achievable even by Enzyme-Linked Immunosorbent Assay (ELISA) methods. Clearly the advent of these new analytical methodologies requires new methods for dealing with the detection of drugs and their metabolites in test samples.

This morning, I’d like to define some of the terms that are used in drug withdrawal and threshold studies; provide some examples of correct use of the terms used in these studies; illustrate various concepts to determine detection time and estimate withdrawal time; describe some of the RMTC sponsored projects that we’re working on at the moment; and give you some recommendations for future work.

The RMTC drug withdrawal studies are aimed to determine the pharmacokinetics of various therapeutic substances in drugs that are used in race track practice. The drugs are administered at clinically relevant doses, and they are administered to exercised and fit thoroughbred horses of racing age. Both geldings and mares are used in these studies. Samples are collected at various times from these horses after administration in order to determine the concentration of the drug and/or its metabolites in the test samples. The concentrations of those drugs and metabolites are determined in two different laboratories using validated LCMS methods. We’re using the latest LCMS methodology so that we are better able to characterize the disappearance of the drug in pharmacokinetic studies as Heather explained just a moment ago.

We are analyzing the data to obtain estimates of various pharmacokinetic parameters. We’re calculating withdrawal times using appropriate statistical techniques. We’re providing this information to various stakeholders for use in decision making. We’re using this approach as one means of promoting uniformity through the adoption of scientifically based thresholds.

Some of the RMTC drug withdrawal studies that have been undertaken to date include studies of p-promazine in thoroughbreds and standardbreds; studies of boldenone in thoroughbreds and standardbreds. Then the remainder of these studies have all been conducted in thoroughbreds; butorfanol, clenbuterol, dantrolene, detomidine, firocoxib, flunixin, fluphenazine, glycopyrrolate, lidocaine, lopivocaine, methocarbamol, nandrolone, pyrilamine, stanozolol and testosterone.

These drugs have been administered. Samples have been collected. Samples have then been distributed to two of the analytical laboratories, and the analytical work is either done or is under way in each case.

Heather mentioned and very adequately described pharmacokinetic studies. Briefly it’s what the body does to the drug and involves processes of absorption, distribution, metabolism and elimination commonly referred to as ADME studies. We use these drug concentrations to establish various mathematical models that can then be applied to other situations. What we learned from these studies is a lot
about the disposition of the drug. What never ceases to amaze me is the substantial animal to animal variability that we see in these studies. I’ll show some real examples of that in a little bit.

Heather also described pharmacodynamics as what the drug does to the body. For many of the drugs that we’re concerned about, the drug interacts either with a receptor or with an enzyme or some macro molecule. Because the occupancy of the receptor site or a binding site on the enzyme is critical to its action. Once all of those receptors are occupied or all the binding sites are occupied, there’s no further increase in drug effect with an increase in concentration.

We typically see this kind of curve as we increase the concentration along this axis and measure the effect along this axis. This is showing 100 percent effect over here, and you can see even with adding additional drug there’s no further increase in drug effect. Again, we see substantial differences from animal to animal in their responsiveness to even the same concentration of drug in the blood sample.

When we integrate the pharmacokinetics and the pharmacodynamics, we can plot the concentration of the drug here and the effect here with 100 percent shown on this axis. Clearly there is a relationship between drug concentration and effect, but that relationship is rather complex. That is part of what Heather was referring to in her presentation. There’s a great deal of complexity in pharmacokinetic and pharmacodynamic studies. We’re attempting to use those studies to determine when or at what concentration a drug is no longer affecting the performance of a horse. These studies are indeed very difficult, very expensive and maybe beyond the reach of what we’re able to do.

In terms of definitions, I want to make sure that we’re using terms correctly. Often times, analysts refer to “analytes” and that’s whatever substance it is that we’re measuring. The limited detection is the lowest concentration of an analyte that can be reliably detected. We can tell that it’s there but we can’t put a number on it that is particularly meaningful. We do these studies by adding drug to urine or plasma and then determining whether we can detect reliably, because we know how much we put in. We know how much that concentration is but we can’t measure that concentration because it’s below the limit of quantitation. This is the limit — or this is the concentration below which the analyte can no longer be reliably quantified. That is below the limit of quantitation. We can’t put an estimate — we can’t reliably determine the concentration of the analyte.

The limit of quantitation is typically two and a half to three times the limit of detection. The limit of detection and the limit of quantitation are characteristics of the analyte. The method that we’ve used to detect it and the values of the limits of detection, and the limit of quantitation can vary considerably from one laboratory to the next. The limit of detection may also vary from day to day, from analyst to analyst in the same laboratory if the method that they’re using isn’t particularly well characterized and controlled on a day to day basis. It is very simple in most cases to modify the limit of detection or the limit of quantitation in the analytical laboratory by making fairly simple changes in the methodology. These aren’t fixed
values. They tend to be more variable in those laboratories that are using methods that aren’t particularly well characterized.

One of the terms that we hear fairly often is the term “trace”. I don’t use the term. It’s a term that doesn’t have a standard definition. It might be used to characterize those concentrations between the limit of detection and the limit of quantitation. Remember, those are concentrations that we can’t put a reliable number on, but we know that the drug is there. Several speakers have talked about zero tolerance. I don’t use the term. I think it is a politically loaded term that really has no significant meaning in the work that we are doing.

The threshold is the concentration above which a finding is reported. That threshold may be the limit of detection. It may be the limit of quantitation. It may be some value set based upon the results of a PK/PD study. It may be a value selected by negotiation like the phenylbutazone threshold of 5 micrograms per ml. Dr. Arthur mentioned the no effect thresholds that were introduced by Dr. Tobin a number of years ago, and these are concentrations associated with no significant effect in the particular model that Dr. Tobin is testing. It may be a local anesthetic effect and so on.

We talk often times about measurement uncertainty. This is a rigorously estimated measure of the uncertainty of a quantitative determination. The measurement uncertainty is always associated with quantitative measurements. The detection time is the last time that a sample concentration is greater than the threshold. Sometimes that’s referred to as the clearance time. Based on — or as a result of information from the detection time, we can establish withdrawal times. These are the times recommended for withdrawal of a drug in order to avoid residues that would be reportable.

I want to talk for just a moment about the RMTC boldenone study. Boldenone undecylenate, name-brand as Equipoise was administered to 20 exercised and fit thoroughbred mares and geldings at the UF Equine pharmacokinetics laboratory. The drug was administered intramuscularly at a dose of 1.1 milligram per kilogram per body weight. One dose was given. Blood and urine samples were collected at pre-determined times after administration, and we measured boldenone concentrations in plasma samples until two consecutive plasma samples contained boldenone in concentrations less than the limit of quantitation.

The plasma samples were analyzed both at UC Davis laboratory and at the University of Florida racing laboratory using validated analytical methods based upon LCMS. As it turns out, we were both using the same instrument, same model of instrument. The sample preparation methods are different, but surprisingly the limit of detection in both laboratories was 10 picograms per milliliter (ml), and the limit of quantitation in both laboratories was 25 picograms per ml. The goal of these studies was to determine the detection time and to calculate a reliable, statistically based withdrawal time.
These are the results of the studies done on those 20 horses. These are plasma boldenone concentrations of picograms per ml. This is 1,000 picograms per ml. That’s equivalent to one nanogram per ml. You can see that some of the concentrations go a little bit above 1,000 nanograms, excuse me, 1,000 picograms per ml. This is 2,000. I have drawn on this slide the limit of detection. You can see that I reported no values less than the limit of detection. This is 100 picograms per ml. This is the time and days and note that this is 50 days, 100 days and 150 days. You can see that boldenone persisted for some considerable period of time after administration of this single dose.

I’ve now drawn on the same slide the limit of quantitation, and you can see that it is substantially higher than the limit of detection. There are no values reported between the limit of detection and the limit of quantitation because, remember, we don’t report values less than the limit of quantitation because they can’t be reliably determined. Are there concentrations of boldenone in these samples below the limit of quantitation? Sure there are, just as there are concentrations below the limit of quantitation, the limit of detection.

The drug continues to disappear. It’s just that we aren’t able, at this point, to measure what those concentrations are. There is at least one racing jurisdiction that has adopted a threshold for boldenone in plasma samples at 100 picograms per ml. You can see there’s a wide range of stopping points, if you will, for boldenone.

This slide then shows the difference in detection times that would result from the application of different limits. One of the differences between the last slide and this one is that I have included here the apparent concentrations of boldenone below the limit of quantitation. This is the limit of quantitation. This is the limit of detection. I was able to put numbers on these samples, but they are less than the limit of quantitation so we didn’t report them otherwise. If we were to use the limit of detection and report all values — report all samples with values above the limit of detection, you can see that the last sample that had a concentration above the limit of detection is here at about 140 days. The last sample with a concentration above this limit of quantitation, on the other hand, is here at 120 days. About a three week difference in this case between a detection time based on limit of quantitation and one based on limit of detection.

If this threshold at 100 picograms per ml is adopted, then the detection period is reduced in this case to 65 or 70 days. If this particular threshold of 300 picograms per ml is adopted, then the detection period is about 25 or 30 days. You can see how the selection of the threshold concentration profoundly affects the detection time.

Based upon the analysis of the data we are able to provide a withdrawal time and it is calculated based on the statistical analysis of the data using a European approach to the determination of milk, excuse me, presence of drugs in milk. We calculate what’s called a 9595 tolerance interval for different threshold concentrations, and then we can calculate and plot the resulting withdrawal time.
What I’ve shown here is the threshold concentration from 25 picograms per ml to about 400 picograms per ml and the corresponding withdrawal time and days. There’s a nice linear relationship, log linear relationship shown here. If one wanted to determine what concentration — regulatory concentration would be required for a particular withdrawal time, one could estimate it from examination of this plot. Should I...?

**Dr. Arthur:** You should wrap it up pretty quick.

**Dr. Sams:** Okay. This slide then shows the time in days required for the plasma concentration of boldenone to fall below the limit of quantitation using a variety of statistical techniques other than the 95% tolerance interval that we showed previously. As one increases the certainty of that determination, the withdrawal time increases. With the highest certainty, the withdrawal time is 162 days. With the least reliable estimate, it’s 146 days. With that I’ll end my discussion and turn it back over to Rick. Thank you.

**Dr. Arthur:** Thank you Rick. Thanks. Our next speaker is Dr. Bobby Lewis, Chairman of the RMTC and past president of the AAEP. Bobby, just a few comments on why withdrawal times and threshold levels are so important.

**Dr. Robert Lewis:** Sure. I don’t have a presentation to make. I’m here to comment and answer questions from the audience about these issues. Some good information that’s been laid out in front of you today by these two speakers, and I just want to highlight a few things that what’s the importance of all this. Well, for years we’ve operated in an environment that’s been one of (a) uncertainty and (b) lack of uniformity from racing jurisdiction to racing jurisdiction. What does that mean? That’s a usual dilemma for trainers that operate in several different jurisdictions, have stables in different jurisdictions, as well as veterinarians who travel from state to state. Quite simply the rules are all over the radar screen.

RMTC was born with its primary objective to try to encourage uniformity among the racing jurisdictions particularly with medication rules, testing methodologies, penalties and enforcement and security measures. The importance of that is it makes life a lot easier for those people who make a living in this sport. It’s an elusive goal but an admirable goal and an achievable goal if we put our mind to it. I think to that end we’ve made some progress. We’ve got a long way to go.

What underpins a lot of this and what we’ve been doing and what our focus has been at RMTC is we became aware very early on that the scientific data out there that would underpin good recommendations for threshold levels and withdrawal times for the various medications that are commonly used on a race track today, the scientific data was lacking. Frankly, it’s fairly shameful with what we’ve had to work with in the past years. We’ve put a lot of effort into trying to eliminate this problem. This is the purpose of these drug administration studies. Number one, they’re done in a significant number of horses. A large enough population of horses that are statistically significant.
Our goal as Dr. Sams laid out is to determine a threshold level and you hear the different terms. No effect threshold. Any term you put on it, it really comes down to this. As a veterinarian, what I want to know is at what level, in a post-race sample for a particular medication, what level represents responsible use of that product? What’s responsible use of that product? That the drug or the medication is available for uses intended, but it’s used in a manner at which we can look anybody in the eye and assure them with confidence that product is not affecting the outcome of a race. It’s having no impact on the horses performance beyond what we intended to use it for to start with and that’s to treat disease and disorders to maintain the health of the horse.

Once we know that levels and that’s not as easy as it sounds because the pharmacokinetics, as they said, studies determine what a body does with a drug. The pharmacodynamics side of it is very, very hard to do. It’s very, very expensive. They have to be extremely well designed to answer the questions that we want answered. Quite simply, as Dr. Sams says, some of them are prohibitively expensive. We’ll never do them. Fortunately there’s been a lot of work done on pharmacodynamics of various medications, and we do have some information in the literature to make those decisions.

Frankly, I hate to use the word “anecdotal experiences”, but they do have a place in this. I think as veterinarians we inherently have an idea of what these various products do to horses. Sometimes we have to lean on that. Our approach to this has been, and it has to be, when you make these decisions, err on the side of caution to protect the integrity of the sport, the integrity of the race. In other words, we don’t want medications that are inordinately impacting the outcome of a race. There are exceptions.

Since this body last met, I doubt the lasix study’s been mentioned other than what’s been read in the press. It hadn’t been on any presentations here I don’t suppose has it? There’s an example of an extremely well designed study on a product that’s used every day in racing. It literally answers some questions that have been asked for 30 years. We now know beyond a shadow of a doubt that furosemide does reduce incidence and severity in lung hemorrhage in the horse. Why is that important? It’s very important for the horse. If you don’t want a horse to bleed, don’t run him. If you’re going to race the horse, a high percentage of them are going to bleed. That’s the inherent nature of that species as an athlete. They’re going to do it.

We owe it to them to protect them against ill effects of that. When we have the scientific knowledge and know how to do that and today furosemide is the one product that we know that can help block that impact of that disease, which is exercise induced pulmonary hemorrhage. Does that impact the performance of the horse? Yes. That question has been asked and answered. No doubt about it, but at least it’s an effect that’s across the board because, literally, anybody can use this product.
There’s an example of, I guess, a tolerable impact on a race that we as veterinarians feel that’s probably a necessary step to make in this industry is to tolerate that impact on a race when you measure the benefits of the product. That would be an exception. Most therapeutic products, we shouldn’t accept that. We should feel that these horses are not having an impact on the day of a race. To get there, we need the threshold levels and withdrawal times to give our trainers and veterinarians a speed limit, if you will. They know if they follow the rules that (a) they will be operating in an environment where people are not critical of the use of these products the way they’re being used; and (b) that these studies are designed that if they do follow the rules, we can tell them with virtual certainty they’ll never get a positive test.

To do that we have to be conservative in our recommendations on what these levels are. For example, with many products if we end up recommending a 72-hour withdrawal time, we inherently know going in that most horses can probably be administered that product at 48 hours and get away with it but not always. You always run the risk of a positive if you try to crowd the rules. That’s biological variance between the horses. You can’t eliminate that because these horses all metabolize and redistribute and clear these products differently. There’s biological variance, and you have to put that into the equation.

This is important to our industry to try to do this. This is the one thing that people that are participating in this industry, as trainers and veterinarians, have asked for — for years is some guidance on how to use these. It’s no secret to most of you. Most racing jurisdictions are very, very reluctant to make a recommendation about withdrawal times on a product. There’s been a reason for that, and I think the biggest reason is scientific uncertainty of what the recommendations are. We owe it to the industry to put some certainty into those recommendations. The only way to do that is to have sound, defensible science.

Going into this Dr. Arthur and I have struggled for a number of years to put a highlight or spotlight on the importance of this. You have to understand that as veterinarians we understand research, and we even pull our hair out at the length of time it takes to accomplish these things but that’s the nature of science. When Dr. Sams does his work, at the end of the day, it has to be able to stand the scrutiny of his peers. These studies have to be well designed, scientifically defensible where there’s no question about his methodologies and the techniques he’s used that are beyond question and are scientifically defensible. You don’t do these with a “shoot-from-the-hip” approach. It takes time and very tedious persistence to develop these studies and make sure they’re done right. The process of once these studies are finished, they’re submitted for peer review and typically published in a research journal somewhere. That’s a time consuming process. Until this has gone all the way through that process, you’re really not complete. You’re talking about a process that takes several years rather than several months.

Nonetheless, we have the ball rolling. He gave you a long list of the products that have currently been studied. The administrations have been done. The analysis
has been done on some. It’s being done on others. We think the outcome of this, over the next several years; we’re finally going to see this process bear some fruit.

Pharmacodynamics studies as far as what the effect of what these products have on an animal, on a horse, need to be done, but you have to crawl before you can walk. We need the pharmacokinetic data first. Pharmacodynamic studies will be needed on some particular products to give us answers as to their true effects on a horse. We are embarking on corticosteroid products. They’re kind of next on the list. They’re a very high profile medication that is widely used. It’s going to be a horrendous or a very enormous task to study these things. It will be expensive and time consuming but we’ll get there. Rick, I think I covered everything pretty well. I don’t have anything to add to it. If you got any questions or the audience has any questions?

Dr. Arthur: I think we need open it up for some questions and hopefully—I would be surprised if we’ve answered everyone’s questions on thresholds so please have at us.

Audience member: Thank you. I’d like to thank the panel. Very good presentation, the substantive and complex issue. I think if the industry, you were to ask people in the industry one thing they would like, why can’t we have a national medication rule with national enforcement? It seems to me like we’re much closer to that than we’ve been certainly in modern times. I’d be interested in your comments on how close are we to a national medication policy or rule including the enforcement aspects of it, the testing and the penalty phase of it? Maybe an example if appropriate on what would be an example of where we are not national in a rule or enforcement. Just sort of get your comments on that issue.

Dr. Arthur: As everyone in this room realizes, the major problem with horse racing is it’s regulated state by state, and every state likes to be a little bit individual. We certainly are closer to a uniform medication policy than we’ve ever been before. I think on the simple drugs like phenylbutazone, flunixin and NSAIDS, I think we’re all fairly close. I don’t think there’s a substantial difference from jurisdiction to jurisdiction.

Probably the urine levels or anabolic steroids were probably as effectively and done as well as any effort in medication that horse racing’s undertaken. On the other hand, the plasma levels look to be very problematic because you have certain states that are running out in their own direction and have already staked their ground out.

Horse racing is inherently against working together, and a lot of it is individual ego, frankly, for different commissions. I do it better than your commission. We see that all the time. For someone that works for a commission, I can tell you that. Particularly you get some individual who wants to be out front, and we see that. I think most of us know an example of which states like to be the first in whatever even though sometimes they end up backtracking.
Any comments from the panel?

Dr. Lewis: I agree with everything Rick said. It comes down to individual personalities in some of these states. They all have, not all of them, but many of them have a test in a laboratory that’s been in place for a long time. They like to think the program they have in their state is the best one. It’s state sovereignty issue I suppose. Until the industry demands that these states fall into line and have some kind of a hammer to produce that effect, it won’t happen.

I will say this though, with a lot of the work we’re doing, we intuitively know that anybody involved in drug testing in America is going to have a hard time hiding from the science; if the science is good science. That’s been lacking in the past. That’s something we’re trying to correct. I think these efforts that we’re making will facilitate a move in that direction as far as testing goes. Testing will drive medication administration rules, but the politics of it is another thing.

The anabolic steroid situation, in the state where we literally saw 36 out of 38 jurisdictions in under 12 months fall into line with regulating these products, was a case study in how to get something done. That was born of a crisis and everybody knows what the crisis was. We know the hammer that affected this. The hammer that was used to affect this is not something that could be used lightly or frequently. Certainly, that was a national issue, which everybody agreed had to be confronted. A lot of these other issues are not quite as sexy, I guess is the best way to put it, so people are not as excited about making the necessary changes as they were on anabolic steroids.

I guess I thought all along it’s an admirable goal to achieve uniformity, and you’re not going to get there by sitting around talking about it. It’s a long process. It takes a lot of hard work by a lot of people. Simply put, we’ve thrown the ball up in the air. RMTC has developed a lot of model guidelines that have been adopted in their entirety by a lot of states, piecemeal in others, not adopted by some. We simply throw the ball up in the air see where it lands and then go back and look at why some of these jurisdictions haven’t adopted them. You just have to develop a strategy and be flexible to try to convince these jurisdictions that it’s a worthy goal to change what they’re doing to fall into line with the rest of the United States.

Dr. Arthur: I think there’s obviously two ways to go. There’s either federal legislation which none of us want; or try to use some of the national hammers we have like the TOBA Graded Stakes issues or Breeders’ Cup. You don’t get a Breeders’ Cup unless you have these particular standards. NTRA accreditation, you may not get accreditation if your state doesn’t meet particular uniform standards. I think we have to be a little bit imaginative, because states go in their own direction. No two ways about it. Yes sir?

Mr. Conrad Cohen: Conrad Cohen, Ontario, HBPA. Couple of questions. Is there a difference between the thoroughbred and standardbred horse as far as dealing with drugs? The other one is, is it fair to use the limit of detection as being a reason for causing a positive test?
Dr. Arthur: Rick, why don’t you handle both of those questions if you don’t mind?

Dr. Sams: Those are two excellent questions and concerns. Because of concerns about differences between thoroughbreds and standardbreds, the USTA and the Hambletonian Society contributed funds to the RMTC to explore just that question. At the beginning of the RMTC work, all of the studies were done in thoroughbred horses. With funding from those two groups, we have done studies in standardbreds that are maintained at the University of Florida and are treated in the same manner as the thoroughbred horses. We have some evidence from the boldenone study that boldenone is cleared from the standardbred horses somewhat more rapidly than it is from the thoroughbred horses. I think there is some preliminary information that there are differences in the rates in which drugs are eliminated in those two breeds.

The second question had to do with is it appropriate to use the limit of detection as the benchmark for reporting positive findings. In my view, absolutely yes for those substances that have no legitimate use on the race track. Fentanyl, for example, should be detected at the limit — should be reported any time it is above the limit of detection, and we should be working on methods to lower that limit of detection. For therapeutic substances, I think the information is compelling that in most cases we should not be using the limit of detection. That’s why these RMTC studies and other studies are directed toward finding what is the appropriate threshold at which findings should be reported.

Dr. Arthur: I would like to point out that this pharmacokinetic data we get, that we can use to give veterinarians and trainers, information to avoid positives can also be used to prosecute cases when obviously a drug was administered within a certain period of time. It’s a little bit of a two-edged sword. This information actually goes both ways, but there are some drugs that you have to be particularly concerned about.

Locally anesthetics, therapeutically used but can they be used to anesthetize an injury on a horse and put a jockey, rider, driver at risk? I think those get to be very, very difficult questions to answer.

Speaker: Just a follow up on the answer Dr. Sams regarding therapeutic medication. As he said the limit of detection is not really satisfactory, but the problem is how can the commissions and race tracks deal with the issue of limit of detection of therapeutic medication as far a penalty to a horseman? It seems unfair when you get to that limit of detection, on therapeutic medications, that horsemen are penalized to the extreme of effective use of those drugs.

Dr. Sams: The issue is when the limit of detection changes, and I will tell you when I started practicing, the withdrawal time for procaine penicillin was three days. It actually got up to over 30 days in California, and it’s now back somewhere around 15 to 20 days even though we recommend pre-race testing for procaine in particular. That is the problem. That’s why we’re trying to set these thresholds.
We know — we’re now testing at picogram levels very readily in blood. We’re going to be looking at femtograms pretty soon. That’s where the technology’s going to go. That’s why we need to set threshold times, because you have 18 different laboratories around the country, and one of them wants to get on the lead on one thing. Ed?

Mr. Ed Martin: I just want to make an observation. I appreciate everybody’s comments about the challenges in achieving uniformity. Sometimes when you come to a symposium like this you come to one meeting and you may not go to another meeting. There was a meeting earlier in the program dealing with interstate compacts. I think people, who have been critical of the regulators for not moving uniformly in certain areas, really need to take a look and embrace a concept that has been discussed for a couple years, by the RCI members and been embraced unanimously by our board, which would be the form of mechanism by which to achieve a certain degree of uniformity.

When you — I would ask everyone in the room, who has over the years complained about a lack of uniformity, to realize that there is a potential answer on the table. I would encourage you to take a look at that and to embrace that. You can complain about uniformity or you can embrace a solution. I just want to make one final observation if I may. I’m not a veterinarian, and I’m not a chemist or a pharmacologist. I’m just pretty much a simple guy. My good friend Bobby Lewis, who I have the honor of serving with on the RMTC board, said something earlier that just kind of — I had to write it down. It’s not something that hasn’t been said in prior forums like this.

It said we need to give our vets guidance on what the dosage should be for the purpose of avoiding tripping a positive. As a layman, that just hit me. I thought the purpose of a veterinarian giving a dosage of any drug was basically to treat an infirmity in the horse. If the motive is to avoid tripping a positive, I just think maybe we all ought to just stop and reflect on that motivation and maybe pull the camera back and really take a good hard look at what we’re doing to ourselves as an industry, to the public perception and perhaps even to the horses given some of the concerns some of our regulatory vets have started bringing forward. I just wanted to make that comment.

Dr. Arthur: Two points. Obviously a national compact has a lot of promise. The second point is I think your response to Dr. Lewis’ comment I think shows how we have a real misunderstanding how veterinarian practice works on the race track. That is, you don’t give a drug to avoid a positive. You give a drug to treat a specific issue. The question is with procaine penicillin, it’s a very — It’s probably the best antibiotic even today to treat the majority of diseases in horse racing. You make the decision when to use that drug based on what that withdrawal time is. That’s true of most drugs, even though I do believe that a lot of drugs are used unnecessarily, but that’s an entirely different issue. One last question and we’re actually out of time.
Mr. Mike Campbell: My name is Mike Campbell. I’m president of the Illinois Thoroughbred Horsemen’s Association. I’d just like to make a comment that I think that the whole industry is in denial about this issue. I’ve trained horses for four years. My whole family has been involved in racing. I’ve seen it all done, and I’m telling you that there are problems with medications violations in the racing community in drugs that are not being detected. You see a pattern of trainers at 40–45 percent of huge test samples changing the performance of horses radically. I see a failure between managements, commissions, security and drug testing facilities that don’t coordinate their efforts to stop these enhancements from taking place.

We’ve got to quit worrying about doing studies on lasix and banamine, drugs that have been in the racing industry and have therapeutic effects, and are well understood and turn our attention to drugs that are synthetic in nature and being used to change the performance of horses. We’ve got to coordinate an effort to where the managements stop not caring about who wins the race. They have no dog in that fight so they don’t look into it in any great detail. They depend on drug testing to solve the issues of trainers taking advantage, because they have greater resources to invest in drugs that change the outcome of the performance of the horse. Thank you.

Dr. Arthur: I understand your comment, and I don’t agree that race tracks don’t have an interest in addressing this issue. In California, it was the race tracks that initiated the TC02 testing in thoroughbreds, which really hadn’t been done uniformly around the country. They started at Del Mar. The response from the whales was, we’re going to come back and bet on your product. Integrity is key to our industry, and I think all of us have to appreciate that. You can organize things. There are big rumors of ractopamine, “pig juice” in quarter horse racing. We went down to Los Alamitos. We shook down every barn, and we did out of competition tests and been looking for ractopamine for months and doing different things, looking in different directions. It can be done, but I will tell you in today’s environment, the race tracks don’t want that full-time employee. The state doesn’t have that full-time employee. A lot of drug testing budgets have been cut. It’s very difficult to do. We basically are going to have to put resources after this, and it’s very, very hard to coordinate these efforts.

I think your point is well taken. I do think super trainers need to be investigated, but you have to do it in a disinterested, objective way. You can’t do it because you don’t like Ricky Dutrow. You have to do it because trainer X has 35 percent wins, and the next guy has 20. Point well taken.

One last question, and we’ll need to break.

Audience Member: Excellent panel. Very well understood. Rick, how are you going to get that information regarding thresholds and withdrawal times to the racing jurisdictions? That’s what I want to know. Are we going to get it as a list at the next RCI annual meeting? Per drug, we get information?
**Dr. Sams:** The process has already started. We’re presenting this information as it is available and has been reviewed.

**Dr. Arthur:** As a matter of fact, Rick, myself, Dan Fick, Scott Waterman are going to meet and try to figure out how to expedite this. It’s very frustrating. We put a lot of money at it. I will tell you, my three years as Equine Medical Director in California, I seldom see a drug positive where somebody has really tried to take a shot at us. Probably less than half a dozen times in three years. Usually it’s a barn screw up where somebody’s made a mistake. There’s a big cost to that in our industry when somebody makes a mistake, because the public doesn’t understand the excuses. All they see are drugs and horse racing. If we can give them better information and hold them accountable for understanding that information. There’s no more excuses, “well I didn’t know what the withdrawal time was”. I actually had a veterinarian older than I am that didn’t understand what the regulation was for phenylbutazone in California. We have to start holding all the licensees that are responsible for violations responsible.

California, we’ve sanctioned a number of veterinarians which hadn’t been done before. You have to go after the people who make mistakes. There has to be consequences to mistakes. In England, they’ve had clenbuterol for 25 years. You don’t see a lot of clenbuterol positives. Why? You get a positive, you have serious consequences. We’ve done that in California. We’ve increased the consequences for those sorts of violations. We’ve had one clenbuterol violation in two years. Southern California thoroughbreds one, none in two years in northern California. Why? There are consequences and now you don’t have a minimum wage employee with his own clenbuterol bottle in his tack box. Those are the things we have to do.

Anyway, thank you very much. There is no “zero tolerance”. We all deal with threshold levels. Every time you go to a bar and drive home, you are dealing with a threshold level, and you have to decide what risk you want to take. Thank you.