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IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA DISTRICT OF CALIFORNIA
SAN JOSE DIVISION

MICHAEL ANGELO MORALES, Plaintiff, v. James E. TILTON, Acting Secretary of the California Department of Corrections and Rehabilitation; Robert L. AYERS, Acting Warden, San Quentin State Prison, San Quentin, CA; and DOES 1-50; Defendants.	**CAPITAL CASE** Case No. C 06 0219 (JF) (RS) C 06-926 (JF) (RS) **SUPPLEMENTAL DECLARATION OF WILLIAM EBLING, Ph.D**

William F. Ebling, for his supplemental submission on behalf of Plaintiff Michael Morales, states as follows:

1. I testified on behalf of plaintiff Michael Morales as an expert in the fields of pharmacokinetics and pharmacodynamics at the hearing held in this action on September 26, 2006. Subsequent to my testimony and after my departure from the hearing, I was informed that Brent Ekins, a clinical pharmacist qualified by the Court as an expert in pharmacology and toxicology, offered certain testimony and opinions that in part responded to my earlier testimony. Counsel for Mr. Morales has requested I submit a supplemental declaration in rebuttal to Dr. Ekins' testimony. I have now read Dr. Ekins' testimony at the hearing and offer these comments for the Court.

2. Dr. Ekins misunderstands the notion of a half-life of a drug. His statement that "Half life is a concept where you have a steady state blood level in a patient, and then we measure half lives" (p.865, l. 15-17), is wrong. Ekins also mistakenly stated that "you can't measure a . . . a half life until you've reached the steady stage." (p. 922, l. 1-3) In fact, there is nothing about the concept of half-life that requires that the drug be at steady state. Half-life exists regardless whether the administration of the drug took place over a long enough duration to come to a constant level (steady state) or whether it is given by bolus injection. This is a fundamental concept that can be found in any textbook of pharmacokinetics. The half-lives reported in the chart contained in the Russo review article were determined after short infusions, the subjects had not reached steady state. In fact, in order to achieve steady state with thiopental, one would need to infuse it for at least 4 terminal elimination half-lives, or almost 48 hours.

3. In response to a question from counsel for Defendants, Dr. Ekins opined that the issue of the half life of thiopental has no particular relevance to the use of the drug in a lethal injection execution given the short "time frame that is usual for these procedures," because "the issue of half life comes into play if you're going to use this for several hours." (p. 866, l. 1-11.) Dr. Ekins' testimony fails to recognize that several half-lives exist for thiopental with different durations and rates, and he confuses the concepts of distribution and elimination half lives. The brief initial

distribution half-lives relevant to a lethal injection execution are those referenced in the chart contained in the Russo paper and are measured in the time frame of minutes. I chose the figure of two minutes to err on the conservative side, although in the execution setting it may be much faster. In estimating the time course of action of thiopental in the body from a pharmacokinetic and pharmacodynamic perspective, the short distribution half-life is the primary determinant of thiopental duration of action after rapid short duration infusions such as administered for anesthetic induction and as sought to be administered in the lethal injection protocol of Procedure No. 770.

4. In his testimony, Dr. Ekins apparently is referring not to the brief distribution half life that occurs at the initial stages, but rather to the elimination or slowest half life, which occurs at the very end of the process and is relevant for the removal of drugs from the body. The time course of thiopental blood concentration decline following rapid bolus administration is characterized by three phases of decline, two rapid distribution phases and a slower elimination phase. The rate of decline in blood concentrations during each phase changes continuously and this changing rate is described with a half-life term which characterizes the time required to decrease the concentration by half. During each time interval equal in duration of one half-life, concentrations will decrease in half. For example, to illustrate how thiopental concentrations decline during the rapid distribution phase, I will use the following example. If we assume that the initial rapid distribution half-life in an inmate is two minutes, then two minutes (or one half-life) after a rapid bolus dose of thiopental the drug concentration will be one-half of the peak concentration that occurred at the end of the bolus dose. After an additional two minutes (or one additional half-life) the concentration will be one-fourth of the peak, and again two minutes later (or three half-lives), concentrations will be one-eighth of the peak concentration. Typical rapid initial distribution half-lives set forth in the Russo chart range from one minute to five minutes depending on the individual. Following a single rapid bolus dose, the rapid initial distribution phase may consist of three to four rapid distribution half-lives, so this

phase can last anywhere from between four and 20 minutes depending on the individual. During this initial phase, peak blood concentrations will decline by 87-94%. After the initial rapid distribution phase, the second, slower distribution phase occurs over the next 40 to 120 minutes, during which typically two half-lives lasting from 20 to 60 minutes each bring the blood concentration level down to less than two percent of the peak concentration level. Finally, the very slow terminal elimination phase occurs, during which blood concentration levels of the remaining thiopental is decreased by half every five to 12 hours. In contrast to the two earlier distribution phases in which thiopental is distributing from blood to muscle, body fat and skin, this later elimination phase is governed by metabolic elimination. It should be noted that brain concentrations track arterial blood concentrations except they lag behind about 30 to 45 seconds) During cross-examination (pp. 877-79, 922-23), Dr. Ekins confirmed that his perspective of half-life is not on the rapid distribution half-lives that are relevant to the evanescent action of thiopental in the first or second distribution phases , but rather that his professional perspective is that of a toxicologist whose focus is on how long it will take for the body to eliminate the burden of an overdose. Clinical toxicologists, like Dr. Ekins, are primarily focused on metabolic or excretory elimination, not on the distribution/redistribution processes relevant in anesthesia. Dr. Ekins apparently does not understand the pivotal role of distribution half-lives in charting the time course of thiopental's ultra-short duration action. He views half-life only in the context of the terminal elimination stage, where a half-life has a duration of up to 12 hours. His conclusions regarding elimination half-lives thus are irrelevant to any discussion about time course of action in anesthesia or execution settings.

5. Dr. Ekins also stated that the variability of the initial half-lives found in the studies was only present if a single dose was given. (p. 936, l. 18--21.) This is an incorrect review of the literature. It confuses variation in the initial half-life times that depend upon patient factors such as age, weight and cardiac output (which is heart rate and stroke-volume), with the more complicated

notion that administration of additional doses of thiopental affects the relative extent by which concentrations will fall within each distribution phase, before progressing to the next distribution or terminal elimination phase. The half-life variability across populations remains regardless of additional doses. The notion that administration of additional doses of thiopental affects the apparent pharmacokinetics of thiopental is as follows: Within any particular individual, if a second dose is added, the extent of fall that will occur during each phase will change to some extent depending on the timing of the second dose, its relative magnitude and the duration of the administration of the second dose. For example, if the initial distribution phase half-life is one minute as was noted for one individual in the Russo chart, and the initial bolus dose is 1.5 grams, the blood concentration will fall for approximately four rapid distribution half-lives before entering the slower distribution phase. During this initial rapid distribution phase, blood concentrations are halved every minute or half-life such that after four minutes the blood concentration will be, in this case, 6.25% of the peak blood concentration . After four half-lives, the rapid distribution phase is exhausted and the remaining 6.25% of the concentrations in the blood will fall according to the second slow distribution phase, and then later the final terminal elimination phase. For a subsequent bolus dose, the initial distribution phase will account for a somewhat smaller percentage disappearance of blood concentrations than the 90 percent reduction in blood concentrations accounted for during the initial distribution phase of the first dose. For example, if a second dose of the same size were administered 10 minutes after the initial dose, the peak concentrations resulting from that dose may fall for three 1 minute half-lives before entering in to the slower distribution phase. (i.e. a fall to 12.5% of this second peak rather than the 6.25% as seen after the administration of the first dose). After the second dose, the remaining 12.5% of the second dose is distributed and eliminated by the slower distribution phase and the terminal elimination phase. In this example the relative contribution of the initial rapid distribution phase to the overall disappearance of the second

thiopental dose was slightly reduced. Although the actual magnitudes of the half-lives (i.e. one to five minutes) however, remains as variable even when additional doses are given. I believe that Dr. Ekins was referring to the long duration infusion situations that he may be more familiar with in the context of clinical toxicology. If thiopental was infused for several hours and then stopped, the resulting decline in thiopental concentrations due to the rapid initial distribution phase, would play a relatively minor role in the overall disappearance of the thiopental concentrations. But of course this infusion scenario is not within the relevant time frame that concerns protocol 770. Therefore, this complicated notion dealing with the relative extent of distribution with repeated bolus doses is not relevant in the execution context. It certainly does not influence variability.

6. If Dr. Ekins' testimony is that the magnitude of half-lives, particularly redistribution half-lives, are dependent on the number of times you administer the drug or the duration of infusion, that testimony also is incorrect. There is no basis or support for this opinion in pharmacokinetics. The magnitude of half-lives of a drug (meaning how long they take to dissipate by one-half) are independent of dose duration or number of doses. This is a first principle in pharmacokinetics. Of course the intensity of effect and the duration of effect are dependent on the dose, the rate of administration and the number of subsequent doses or infusion regimens. In this sense the time course and intensity of thiopental's action is "context sensitive" and depends on how the drug is administered, including any previous doses in the case. A major part of the training of anesthesiologists is the development of the appreciation of the fundamental properties of the drugs and how they are expected to respond within these administration contexts, as well as the ability to effectively respond in light of those contexts. However, the fundamental half-lives of thiopental do not change.

7. Dr. Ekins' suggestion that my past thiopental studies have utilized an inappropriate one-compartment physiologic model (p.867, l. 9-15) demonstrates a profound lack of familiarity

with my past work and analysis. Neither I nor my professional collaborators have ever stated that thiopental is capable of study using a one compartment model, indeed in our physiologic models we routinely employ more than 10 compartments. Dr. Ekins apparently misunderstands the concept of an effect compartment, which is a representation of the site of *effect* as a single compartment such as the arterial blood supply or the brain. That site is connected to the rest of the body, which is of course multi-compartmental. All of the studies recognize this and account for it.

8. If Dr. Ekins is attempting to state that the studies I participated in only measure arterial blood supply, that is incorrect as well. Many measure brain functioning. Further, the relationship between the arterial blood supply and the brain is well-known and is factored into any modeling. In the case of thiopental, we know the amount of time it takes to reach the brain, and to redistribute out, and the rate at which it does this, all in relation to the arterial blood supply.

9. Dr. Ekins' discussion of the use of thiopental to maintain anesthesia (p. 867-68) ignores the operative mode of use of thiopental in Procedure No. 770. In the lethal injection protocol, thiopental is effectively being used to *induce* anesthesia using a bolus dose. Thus, in Procedure No. 770, thiopental is being used with the same intent that an anesthesiologist administers thiopental in a surgical procedure to *induce* anesthesia. In both types of procedure, the drug is administered over a relatively short period of time rather than through prolonged infusion. The initial distribution/redistribution process (the first and second phases) predominate at a minimum for at least the first 40 to 120 minutes after the initial injection. Thiopental does have the slower elimination half-life as Dr. Ekins has referred to, however, this half-life does not significantly influence the time course of thiopental's concentrations for at least 45 minutes after the initial injection. By that time, the concentrations are so low that thiopental's pharmacologic action has dissipated. This slow elimination phase is not relevant in the context of execution.

10. Dr. Ekins' discussion of maintaining anesthesia levels with thiopental is related to a continuous infusion model, which, in Procedure No. 770 comes in the form of an IV drip. This, however, is not the type or amount of dosing that affects the initial redistribution half-life in an execution, and none of the literature he cites states otherwise. First, because of the timing involved and the length of tubing, that drip does not deliver thiopental to the body until after the potassium chloride is administered through the IV. Second, it will take a while for that constant rate drip to achieve the elevated levels of thiopental required to fill in a developing "gap" of inadequate thiopental concentrations that potentially could result from the redistribution of the bolus dose. Thus, a gap in anesthetic coverage can occur as the initial dose is redistributed, but before any thiopental from the drip has had the opportunity to "catch-up" and accumulate to sufficient levels to refill the gap. The DP Crankshaw 1985 paper that Dr. Ekins cites comes to the conclusion that a complex infusion scheme that varies the rate is required to insure appropriate thiopental levels in an infusion context. Procedure 770 uses only a simple infusion scheme in an attempt to maintain anesthesia and therefore increases the risk that an inmate will not be properly anesthetized.

11. Dr. Ekins testified that he is not aware of any studies measuring the levels of thiopental in the brains of animals (p. 869, l. 2-5), although he also testified that after being deposed by counsel for Mr. Morales he read an article that I co-authored with Wada (p. 863, l. 17-18). In fact, that article concerns the physiological model of thiopental in the rat and contains more than 70 determinations of brain levels of thiopental in rats. By measuring the arterial blood concentrations and the brain concentrations and by conducting contemporaneous EEG readings following administration of doses of thiopental, we have been able to correlate brain concentrations with drug effect and have been able to chart the time course of the drug in the body as the thiopental moves from arterial blood into brain and back into the veins. Dr. Ekins' testimony reflects inattention to the article which he claims to have read as well as unfamiliarity with other learned studies and literature

in the field which have established the time course of thiopental in the body. It is standard knowledge today in anesthesia how quickly blood and brain concentrations track Thiopental research conducted using principles of pharmacokinetics and pharmacodynamics has measured blood and brain concentrations and monitored EEG activity in animals, and measured blood concentrations and EEG changes in man, and correlated the data to determine how the blood and brain concentrations track and what brain concentrations are required to produce different levels of anesthesia in man. This was the principle in Gustofsson's two articles, on which I was a co-author, and the Wada article. These and other works of my collaborators have been repeatedly as examples of seminal clinical pharmacology studies that have led to our understanding of the determinates of thiopental action.

12. Dr. Ekins' statement that the lethal injection drip "simply replace[s]" the thiopental that has been distributed from the bolus dose indicates a lack of understanding of the procedure and the time course of thiopental, and a misreading of the literature he cites. First, as stated above, because of the length of the IV tubing used for the continuous drip, the thiopental administered by the drip will not enter the inmate's veins until four or five minutes after the intravenous infusion has been started, assuming flawless administration, with the result being that the drugs administered by the drip will not enter the inmate's veins until after the potassium chloride has been administered in many inmates. Second, Dr. Ekins' suggestion that a constant intravenous infusion will result in the replacement of what is removed from the initial bolus dose would be correct only if the drug being administered exhibited one-compartment pharmacokinetic behavior. Thiopental has at least three phases and even Dr. Ekins testified that it has four or five compartments. While using a loading dose followed by steady state infusion to instantaneously achieve and then maintain a constant concentration would be effective with a one compartment drug, for multi-compartment drugs the infusion rate cannot be constant but must vary continuously with time to maintain concentrations. In

recognition of this principle, it is standard practice to use computer-controlled infusion pumps in anesthesia to maintain constant levels of anesthetics, as the computer-controlled infusion pumps incorporate the pharmacokinetic model of the drug, and continuously vary the infusion rate of the drug to "clamp" the concentration at the desired level. The single rate infusion paradigm set forth in Procedure No. 770's drip and endorsed by Dr. Ekins will not be able to keep up with the rapid multi-phase distribution of the thiopental (first or second phases) and therefore concentrations could fall dramatically for some period of time with this technique. While Dr. Ekins contends that the three articles he reviewed after his deposition confirm the viability of the technique proposed in Procedure No. 770 (p. 947, l. 18 to p. 948 l. 7), those articles in fact all refer to the fact that thiopental must be infused with a complex changing infusion rate to maintain constant concentrations, a far different protocol than provided under Procedure No. 770. In Procedure 770, the IV drip dose will not be sufficient to catch the falling bolus dose for some time for several reasons. Most important are the timing of the drip, and the fact that the bolus dose is given over a period of three to four minutes, rather than the 10 to 15 seconds it is routinely administered and which is assumed in the studies. And, the articles he relied upon to state that the drip is twice the level that would be used in surgery is misleading because thiopental is not used by itself to maintain anesthesia.

13. Dr. Ekins' testimony that delivery of 1.5 grams of thiopental would result in a surgical level of anesthesia within one minute and would produce a pain-free execution (p. 871) demonstrates that he does not understand the nature of anesthesia practice, which relies on the complex interaction of several drugs administered at the right doses and the right times to create surgical anesthesia. In clinical practice, thiopental is not used as a maintenance anesthetic, but rather as an induction agent, usually with an induction dose of a narcotic, to initiate anesthesia to allow the anesthesiologist to insert a tube across the vocal cords and into the trachea to support breathing, a procedure that takes about 30 seconds. Only for those 30 seconds must the thiopental work to block consciousness and

create such profound brain depression that the brain cannot respond to this noxious stimulus. Once the tube has been inserted, the anesthesiologist starts the maintenance anesthesia, usually using a combination of nitrous oxide and a narcotic, and perhaps a potent vapor anesthetic such as isoflurane. Unlike thiopental, all of these maintenance anesthetics have good analgesic effects, with the effects exceptionally good when a narcotic is used. After induction, the effect of thiopental dissipates rapidly and the ability of the drug to continue to ablate response to the insertion of an endotracheal tube (which is a less painful stimulus than a potassium chloride injection) is gone in approximately two minutes, and the narcotics and nitrous oxide take over the role of maintaining anesthesia and producing analgesia.

14. Moreover, Dr. Ekins' testimony that the doses of thiopental would create a pain free procedure misrepresents how the execution procedure relates to the procedures employed in the clinical practice of anesthesia. The two procedures are not equivalent. Procedure No. 770 uses a single anesthetic, an ultra-short acting induction agent with very poor analgesic activity, with no other drugs used to maintain anesthesia and produce analgesia. In contrast, in a surgical setting, a whole tool kit of drugs is available to induce and maintain anesthesia and analgesia. Dr. Ekins in effect takes the position that procedures such as opening the chest cavity in cardiac surgery are being performed using only an induction dose of thiopental without any other anesthetics. Dr. Ekins's testimony demonstrates a lack of understanding of the nature of anesthesia practice and a lack of recognition that thiopental is not an analgesic, but must always be supplemented with a narcotic to get adequate analgesia control.

15. Dr. Ekins relies on the Gentry article for the proposition that only at slow infusion rates is dose requirement dependent on rate (p. 895, l. 10-11), but in doing so he fails to appreciate the unique challenges raised by a lethal injection execution. Dr. Ekins' conclusion fails to take into consideration the end point or target level of anesthetic depth and the target concentration levels

associated with the target being studied by Gentry. These are very different levels than required to conduct an execution. The endpoint studied in the Gentry paper is extremely light, focusing on the level of unconsciousness at which a subject will drop a syringe, a level in fact very close to the subject being awake with eyes open, with a thiopental concentration level of approximately 4 ug/ml. To employ the Gentry studies in the context of execution dose requirements, one must first take into consideration the depth of anesthesia required in the execution context. This is not dropping a syringe. Second one must take into consideration the infusion rates required to meet this execution requirement. Because of linear first order principles one can legitimately scale the results of the Gentry paper to the execution context to determine the range of infusion rates where rate influences dose requirement. In the context of an execution, we need to reach and maintain for at least thirty minutes a concentration that will continue to ablate awareness through the flush, the administration of pancuronium, and the concentrated potassium chloride injection, as well as through any delay between the end of the thiopental injection and the start of the potassium chloride injection. Such a concentration is at least in the burst suppression range, or at a minimum at least ten times higher in concentrations than required to achieve syringe drop in the Gentry studies. Because he used such a low threshold for affect (4 ug/ml), and a much higher one is required for executions (at least 40 ug/ml), the infusion rates that are required to achieve execution ready levels will be at least 10 times higher than those used in Gentry. In Gentry, the infusion rate was 40 mg/min and below but this is in the context of the Gentry endpoint. Therefore, with execution endpoints, the Gentry paper confirms that the sensitive rates must be at least as high as 400 mg/min. Rates at least as high as 400 mg/min are thus in the range where infusion rates play a significant role in determining dose requirement. Accordingly, in the execution context the effectiveness of a given dose will be affected by the rate of administration.

16. Another feature of this article that Dr. Ekins fails to consider is the effect of extended administration of the initial bolus dose over several minutes. The article clearly notes that this reduces peak effect significantly. This is not what happens in the surgical setting, as the bolus doses are given in 10 seconds or so. Thus, uncontrolled administration rates as in Procedure No. 770 will lead to an elevated risk that the inmate was sufficiently anesthetized during the execution to withstand the noxious stimulus of the potassium chloride.

17. Contrary to Dr. Ekins' testimony (p. 923), the protocol in Procedure No. 770 is equivalent to giving only a single bolus dose of thiopental to the inmate. The single bolus dose is administered over 2 minutes in the most optimal circumstances, which appears to have been accomplished very rarely in previous executions, but because of the length of line and slow drip, it does not fully reach the inmate for several minutes. The drip infusion is started one minute later which delivers additional thiopental to the patient four to five minutes later. With clinical doses used to induce anesthesia, the duration of burst suppression is about 1 minute. In the context of a lethal injection the question is whether the 1.5 gram dose of the thiopental will maintain burst suppression levels of unconsciousness before the pancuronium and potassium chloride are delivered to the inmate. Thus in the surgical setting, the anesthesiologist has a very narrow window of time to intubate the patient; in an execution context, the state has a very narrow window in which to kill the inmate before his blood concentration levels are below burst suppression and he could feel the suffocation form the pancuronium and the pain of the potassium chloride injection.

18. Dr. Ekins' testimony that blood concentration levels of thiopental of 13-15 ug/ml are necessary to perform surgery is misleading and relies on research results taken totally out of context. In the studies relied upon by Ekins, thiopental was used to induce anesthesia but the patients also received a maintenance anesthetic consisting of a very high dose narcotic with nitrous oxide. Accordingly, the concentration levels recognized in these studies cannot be used as a guide for what

amount of thiopental as the sole anesthetic agent is required to block pain in an execution because the published levels are recorded in a surgical maintenance context with many different drugs. In such a setting, thiopental concentrations would be lower because the majority of the anesthesia is coming from the narcotic infusion and the nitrous oxide, another anesthetic. It should also be noted that this study relied on venous concentrations, which are much lower than arterial concentrations and not a reliable method of measuring blood level as it relates to level of unconsciousness.

I declare under penalty of perjury under the laws of the State of the United States that the foregoing is true and correct. Executed this 9th day of November 2006 in Newark, Delaware.

___William F. Ebling /s/_____

William F. Ebling, Ph.D