

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ANESTHETIC & LIFE SUPPORT
ADVISORY COMMITTEE

87TH MEETING

+ + +

Tuesday, January 12, 1999

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The Advisory Committee met in the Center

for Drug Evaluation and Research Advisory Committee Conference Room at 5630 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Terese Horlocker, M.D., Chairperson, presiding.

PRESENT:

- TERESE HORLOCKER, M.D. Chairperson
- MICHAEL ASHBURN, M.D.
- AMANDA S. CARLISLE, Ph.D., M.D.
- MARIA CONNOLLY, D.N. Sc.
- WINSTON C.V. PARRIS, M.D., FACPM
- JOSEPH REVES, M.D.

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ORIGINAL

PRESENT (Continued):

CHARLES ROHDE, Ph.D.

JOHN SAVARESE, M.D.

RICHARD SMILEY, Ph.D., M.D.

TOBIN, JOSEPH, M.D.

MEHERNOOR WATCHA, M.D.

KATHLEEN REEDY, Executive Secretary

CONSULTANT PRESENT (non-voting):

JOHN DiMARCO, M.D.

INVITED GUESTS PRESENT:

ANWAR GOHEER, M.D.

CYNTHIA MCCORMICK, M.D.

THOMAS PERMUTT, Ph.D.

BOB RAPPAPORT, M.D.

MONICA ROBERTS, M.D.

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1 P-R-O-C-E-E-D-I-N-G-S (9:00 a.m.)

2 **Call to Order and Opening Remarks**

3 DR. HORLOCKER: Good morning. I'm Terese
4 Horlocker. I would like to call this meeting to
5 order.

6 Today we will be speaking about
7 Chirocaine, a levobupivacaine derivative, a long-
8 acting, local anesthetic.

9 I think the search for a long-acting,
10 potent, reliable, local anesthetic started back in the
11 1970s after the initial reports of cardiac toxicity
12 and difficult resuscitations after bupivacaine
13 toxicity in parturients that had received greater than
14 .5%.

15 Preliminary data suggested that
16 levobupivacaine was of similar efficacy, but had less
17 toxicity, and when the Company approached the FDA
18 initially, they requested that the black box be
19 removed from the labeling of Chirocaine when the drug
20 was eventually approved.

21 An Advisory Committee meeting was held in
22 March of 1997 to discuss, among other things, labeling

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1 issues, and specifically at that time, the Sponsor
2 requested that the Advisory Committee tell them what
3 information would be needed to remove this black box
4 label, and also what additional data would be needed
5 for them to be able to make the claim that Chirocaine
6 was less toxic than racemic bupivacaine.

7 I think most of the groundwork discussion
8 was performed during that meeting. The
9 recommendations included that there should be
10 additional clinical and laboratory studies done;
11 specifically, finding at least a 25% reduction in
12 cardiac toxicity in one study, and also the Committee
13 members at that time requested that additional
14 obstetrical and pediatric patients be studied.

15 So, at this point in time, we are ready to
16 go over the results of those studies, and evaluate
17 Chirocaine for approval and discuss the additional
18 labeling issues.

19 At this time, I would like to have the
20 Committee members introduce themselves, perhaps just
21 a quick, your name, where you are from.

22 Introduction of Committee

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1 I'm Terese Horlocker. I'm from the Mayo
2 Clinic. I am an Associate Professor there. Dr.
3 Reves?

4 DR. REVES: Jerry Reves from Durham, North
5 Carolina.

6 DR. SMILEY: Rick Smiley from the
7 University of New York.

8 DR. CARLISLE: Sue Carlisle, University of
9 California, San Francisco.

10 DR. ASHBURN: Michael Ashburn, University
11 of Utah, Department of Anesthesiology.

12 DR. WATCHA: Mehernoor Watcha, Children's
13 Hospital, Philadelphia, University of Penn.

14 DR. TOBIN: Joe Tobin, Department of
15 Anesthesia and Pediatrics, Wake Forest University
16 School of Medicine, Winston-Salem.

17 DR. DiMARCO: John DiMarco, Cardiac
18 Electrophysiologist from the University of Virginia.

19 MS. REEDY: Kathleen Reedy, Executive
20 Secretary, Food and Drug Administration.

21 DR. ROHDE: Chuck Rohde, I'm Professor of
22 Biostatistics at Johns Hopkins.

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1 MS. CONNOLLY: Maria Connolly, Associate
2 Professor of Medical-Surgical Nursing, Loyola
3 University, Chicago.

4 DR. SAVARESE: John Savarese, Cornell
5 University, New York Presbyterian Hospital.

6 DR. GOHEER: Anwar Goheer, Pharmacologist
7 at the FDA.

8 DR. ROBERTS: Monica Roberts, Pediatric
9 Anesthesiologist, FDA.

10 DR. RAPPAPORT: Bob Rappaport, Deputy
11 Division Director.

12 DR. MCCORMICK: Cynthia McCormick,
13 Director, Division of Anesthetics, Critical Care and
14 Addiction Products, FDA.

15 DR. HORLOCKER: Ms. Reedy, would you like
16 to read the Conflict of Interest Statements?

17 **Conflict of Interest Statement**

18 MS. REEDY: Conflict of Interest Statement
19 for the Anesthetic and Life Support Drug Advisory
20 Committee, January 12, 1999.

21 The following announcement addresses the
22 issues of conflict of interest with regard to this

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1 meeting, and is made a part of the record to preclude
2 even the appearance of such at this meeting.

3 Based on the submitted Agenda and
4 information provided by the participants, the Agency
5 has determined that all reported interests in firms
6 regulated by the Center for Drug Evaluation and
7 Research present no potential for a conflict of
8 interest at this meeting.

9 In the event that the discussions involve
10 any other product or firms not already on the Agenda,
11 for which an FDA participant has a financial interest,
12 the participants are aware of the need to exclude
13 themselves from such involvement and discussion, and
14 their exclusion will be noted for the record.

15 With respect to all other participants, we
16 ask in the interest of fairness that they address any
17 current or previous involvement with any firm whose
18 products they may wish to comment upon.

19 DR. HORLOCKER: Dr. McCormick, would you
20 like to make your opening comments, please?

21 I would also like to state at this time
22 that our discussions can occur at the end of

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1 presentations; however, if someone needs to make a
2 clarification, we could interrupt the speaker at that
3 point in time, only.

4 Opening Remarks

5 DR. MCCORMICK: Thank you. Dr. Horlocker,
6 Committee members, sponsors of levobupivacaine,
7 consultants, members of the public, and FDA staff.
8 Good morning, and welcome to the January 12th, 1999
9 meeting of the Anesthetic and Life Support Advisory
10 Committee.

11 Dr. Horlocker, we have asked you and our
12 Advisory Committee to meet with us today to provide
13 advice to the FDA on a subject of very narrow focus,
14 as we prepare to take action on this product over the
15 next month.

16 We are not specifically seeking your
17 advice about the risk-to-benefit ratio of this
18 product, as we have reviewed the Sponsor's materials
19 and data on the clinical development in the NDA, and
20 we are satisfied that these criteria have been met.
21 Instead, we would like to limit your focus and
22 discussion on the cardiovascular safety of this

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1 product.

2 We have provided for you reading
3 background materials that include the transcripts from
4 three advisory committee meetings, all of which have
5 relevance to today's meeting. We had hoped to see an
6 agent emerge with the efficacy of bupivacaine without
7 the cardiovascular side effects.

8 We have considered how we might gain
9 assurance, since we can never be absolutely certain,
10 that a product indeed might have a more favorable
11 safety profile.

12 As you will hear from the Sponsor today,
13 there is a strong theoretical basis for postulating a
14 differential toxicity between racemic bupivacaine and
15 the enantiomer on cardiovascular toxicity.

16 The early preclinical work is quite
17 compelling. How this unquestionable, theoretical
18 advantage translates into a clinically meaningful
19 advantage has been a matter for our review team to
20 grapple with.

21 In some preclinical studies, for example,
22 the catheterized ewes studies which Dr. Mather no

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1 doubt will discuss today, IV levobupivacaine was
2 capable of causing the very same cardiovascular
3 effects attributed to bupivacaine, but at a higher
4 dose.

5 How does this dose separation for toxicity
6 extrapolate in a practical way to the human or
7 clinical situation, or does it? And at what doses
8 does one expect to see significant human
9 cardiovascular toxicity? At what concentrations, and
10 in what setting? And will they be achieved in the
11 normal course of anesthesia or pain management?

12 You will hear that, in an FDA database of
13 nearly 1500 subjects and patients, there was not an
14 identifiable difference between the safety profile of
15 levobupivacaine and bupivacaine, not even in the
16 studies designed to focus on subtle EKG changes, so
17 the differences remain largely theoretical.

18 In 1997, this Committee deliberated on the
19 development of this product prospectively. The
20 Sponsor has completed some of these studies which you
21 have recommended, and they will discuss these results
22 today. The remainder of the studies are either

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1 awaiting completion, or have not yet begun.

2 The question you will be asked to help us
3 with, given the background materials and the
4 preclinical and clinical data submitted is, to
5 paraphrase the question actually submitted, does the
6 existing data support a lesser warning than exists for
7 bupivacaine? And if so, what evidence is most
8 compelling for you?

9 If not, should further study be
10 undertaken? And will the satisfactory completion of
11 the preclinical studies yet to be performed contribute
12 to changes in the warnings that currently exist in the
13 bupivacaine label for this product?

14 Remember that a product's labeling is the
15 FDA's tool for informing the public through the
16 prescribing physician and directly, about the
17 product's potential risks.

18 Every fact that is or is not disclosed in
19 the labeling makes a statement. What goes into the
20 labeling should be an accurate, truthful synopsis of
21 what we know or don't know, based on the data
22 presented to us in the NDA.

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1 While you may no doubt be aware of the
2 effects of your decisions on the marketplace and
3 clinical practice, keep in mind that CDER's mission is
4 to make safe and effective drugs available to the
5 American people, so let science inform your
6 deliberations and let the public safety guide your
7 judgments and recommendations.

8 Thank you.

9 **Open Public Hearing**

10 DR. HORLOCKER: Thank you. At this point
11 in time, is there anyone that would like to speak as
12 part of the Open Public Hearing? Very well. We can
13 proceed then with the Sponsor Presentation, if you are
14 prepared.

15 **Sponsor Presentation: Introduction,**
16 **Rationale, Agenda**

17 DR. GENNERY: Dr. McCormick, members of
18 the FDA Division, Dr. Horlocker, and members of the
19 Advisory Committee, my name is Dr. Brian Gennery. I
20 am the Medical Director of Chiroscience, and also the
21 Project Leader for the product that we are discussing
22 today, Chirocaine, or levobupivacaine.

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1 First of all, I would like to say how much
2 we at Chiroscience appreciate the opportunity of being
3 invited to this meeting and share with you our ideas
4 and data on levobupivacaine that has been developed
5 over the last two to two and a half years.

6 I also want to make it clear that all of
7 the speakers here who are here on behalf of
8 Chiroscience, are consultants or investigators to whom
9 we have paid fees, expenses, and where appropriate,
10 funding for their department in order to carry out the
11 research programs.

12 If I may spend just a moment about telling
13 you who we are, because various names appear in the
14 documentation. Chiroscience Group plc is an emerging
15 bio-pharmaceutical company based in Cambridge in the
16 United Kingdom, and Seattle in the United States.

17 Darwin Discovery is the Research and
18 Development subsidiary within Chiroscience, but for
19 today, we will refer to the name, Chiroscience,
20 throughout.

21 I would like to spend a moment or two
22 describing to you the rationale for developing

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1 levobupivacaine.

2 You are very familiar with bupivacaine as
3 a potent, long-acting, local anesthetic with more than
4 20 years experience in clinical practice, having
5 excellent sensory block and a good motor-sensory
6 separation ratio; however, its use has been clouded by
7 the occasional episodes of central nervous system and
8 cardiovascular toxicity, which has occurred very
9 largely in overdose, which is usually presumed to be
10 an unintentional intravascular injection.

11 And this has led to the boxed warning here
12 in the United States such that 0.75% concentration of
13 bupivacaine is not permitted for use in the obstetric
14 patient. And similar warnings exist throughout most
15 countries throughout the world.

16 There was some evidence in the literature
17 that the dex enantiomer of bupivacaine has a higher
18 potential for causing both the CNS and the CVS
19 toxicity than the levo enantiomer, and therefore it
20 seemed to make some sense to try and develop the levo
21 enantiomer.

22 More encouraging than simply this fact,

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1 was also that there was some evidence that the levo
2 enantiomer had the same efficacy as the racemate when
3 used in the clinic.

4 Thus, our objectives, which were partly
5 formed after our discussion with this Committee nearly
6 two years ago for which we were very grateful to have
7 that guidance, was this.

8 To demonstrate in animals and humans that
9 there is a diminished risk of CNS and cardiovascular
10 toxicities if levobupivacaine is administered by an
11 unintentional intravascular injection, when compared
12 to bupivacaine at the proposed therapeutic doses.
13 Obviously, with humans, we couldn't go above a certain
14 dose, for ethical reasons.

15 And we agreed at that meeting that
16 something like a 25% difference, at least a 25%
17 difference, would be required to satisfy the Committee
18 that an objective had been achieved. And whilst that
19 was relatively easy to plan into protocols in animal
20 studies, it of course was much more difficult within
21 the human studies, although we believe we have tried
22 to keep within the spirit of that discussion.

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1 We also wished to demonstrate that
2 levobupivacaine had an equal anesthetic effect when
3 used at the same concentrations and volumes as
4 bupivacaine.

5 And in our clinical trial reports, we
6 tried to avoid the use of the word, potency, per such,
7 but, equal anesthetic effect. We have described
8 potency in the preclinical section of the NDA with a
9 variety of animal experiments.

10 We also wish to provide a comprehensive
11 data package to the practicing clinician illustrating
12 the use of levobupivacaine in a variety of surgical,
13 pediatric, and pain management studies.

14 We clearly recognized the challenging of
15 the labeling discussion that would occur, and indeed
16 was pointed out at the meeting two years ago.

17 We believe that the data will show that
18 the potential for cardiovascular and central nervous
19 system toxicity of levobupivacaine has been adequately
20 evaluated at the proposed therapeutic doses.

21 And the differences between
22 levobupivacaine and bupivacaine will show that the

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1 boxed warning would not be appropriate for
2 levobupivacaine.

3 Our presentation this morning will focus
4 on a broad range of preclinical studies which
5 consistently show at least a 25% difference in
6 cardiovascular toxicity between the racemate and
7 levobupivacaine; human studies showing differences in
8 both central nervous system and cardiovascular system
9 toxicities between the two products; and a review of
10 the clinical trial database to include the limited
11 experience we have of inadvertent accidental
12 intravascular administration, and we have now
13 completed a meta-analysis of EKG data which was
14 submitted as individual studies within the NDA.

15 Our Agenda is here. Dr. Robert Gristwood,
16 who is a consultant in biology to Chiroscience, will
17 present to you preclinical data in both in vitro and
18 in vivo studies.

19 Professor Laurie Mather from Sidney,
20 Australia will describe his sheep model, and also
21 comment on the work that Dr. Alan Santos has done, who
22 unfortunately couldn't be with us today.

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1 We will then move on to a discussion of
2 clinical data; human volunteer studies looking at
3 cardiovascular parameters will be introduced by Dr.
4 Walter Nimmo.

5 And then the clinical trial experience in
6 terms of efficacy will be described by Dr. Kopacz and
7 an overall view of safety by Dr. James Crews.

8 And finally, I will try and bring it all
9 together at the end of our presentation. I would now
10 like to hand over to Dr. Gristwood.

11 **In Vitro and In Vitro Studies**

12 DR. GRISTWOOD: Good morning, ladies and
13 gentlemen. My name is Robert Gristwood. I am a
14 pharmacologist-biochemist, currently acting as a
15 biology consultant to Chiroscience on the
16 levobupivacaine development program. I have been
17 associated with that program for the past five years.

18 In my presentation today, I am going to
19 review preclinical evidence that levobupivacaine is
20 less cardiotoxic than racemic bupivacaine.

21 Okay, cardiotoxicity has been a concern
22 for bupivacaine in the clinic, and the seriousness of

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1 this has been indicated by the very large number of
2 preclinical studies that have been carried out to look
3 into the etiology of the cardiotoxicity.

4 And these have shown that bupivacaine can
5 have both direct and indirect effects on the heart,
6 the indirect effects largely arising through
7 interactions with the central nervous system, but
8 there are a large number of direct effects.

9 And these include blockade of cardiac ion
10 channels including sodium, potassium, and calcium
11 channels, which result in mechanical changes,
12 reduction in contractility; electrical changes,
13 changes in action potential configuration; conduction
14 delay, abnormal EKGs and arrhythmias; and also,
15 decreases in heart rate.

16 As you know, bupivacaine is a racemic
17 mixture of levobupivacaine and dexbupivacaine, and
18 there is good evidence that bupivacaine cardiotoxicity
19 is enantiomer-selective.

20 And data from preclinical studies I
21 believe clearly show that levobupivacaine is less
22 cardiotoxic than both the racemate and dexbupivacaine.

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1 An important question is, how much less
2 cardiotoxic should levobupivacaine be than the
3 racemate, in order to confer a clinical advantage?

4 And this question was discussed at the
5 ALSDAC meeting in March 1997, and the outcome from
6 that meeting was that the Committee would like to see
7 more than one preclinical model predicting a
8 substantial, defined as 25% or greater, difference
9 between the bupivacaine enantiomers, and between
10 levobupivacaine and racemic bupivacaine.

11 Data from the preclinical studies has been
12 summarized in a table, which is included in the
13 Briefing Document and the NDA, and what I am going to
14 do now is take you through the table, looking at
15 effects on cardiac ion channels, and looking at
16 toxicity on isolated whole hearts, and then moving on
17 to look at cardiotoxicity in intact animals.

18 Okay, so this shows the cardiac ion
19 channel data. The layout of the table is as in the
20 documentation; it shows the parameter, the species
21 from which the data were obtained, and the relative
22 cardiotoxicity of dexbupivacaine to levobupivacaine,

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1 and racemic bupivacaine to levobupivacaine.

2 And the relative cardiotoxicity is defined
3 by the percentage by which dex and racemic bupivacaine
4 exceeded the cardiotoxicity of levobupivacaine, where
5 0, a 0% would indicate that there is no difference
6 between the two.

7 A positive value tells us that
8 levobupivacaine is less cardiotoxic, the bigger the
9 value, the greater the advantage for levobupivacaine.

10 Okay, so here we have data for cardiac
11 sodium channels and cardiac potassium channels.
12 Sodium channel data was obtained using guinea pig
13 myocardium, which is considered to be a good model of
14 human myocardium.

15 Three studies were obtained with this; two
16 compared dexbupivacaine with levobupivacaine, and one
17 compared racemic bupivacaine with levobupivacaine.

18 Looking at this column, first of all, the
19 first study, which was a functional study, showed that
20 dexbupivacaine was 140% more toxic than
21 levobupivacaine on the sodium channels.

22 In this study, it was also shown that not

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1 only was dexbupivacaine more potent in its ability to
2 block sodium current, it also bound faster and
3 unblocked more slowly than levobupivacaine, which are
4 important kinetic considerations, indicating further
5 advantages for levobupivacaine.

6 In this study, which looks at sodium
7 channels, it was found that dexbupivacaine was 66%
8 more toxic than levobupivacaine.

9 In the study comparing racemate with
10 levobupivacaine, it was found that the racemate was
11 54% more toxic than levobupivacaine.

12 These are data from the Chiroscience
13 study, and I will show some values in a moment from
14 this study.

15 For the cardiac potassium channel study,
16 a study was carried out using human HKV 1.5 delayed
17 rectifier potassium channels, and it was found that
18 dexbupivacaine was 560% more toxic than
19 levobupivacaine on the channel.

20 I would just like to point out that there
21 are possible interactions between the channel
22 blockade, and it is known that under certain

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1 circumstances that potassium channel blockade can
2 actually intensify and prolong sodium channel
3 blockade, so this value for dexbupivacaine could
4 actually feed back and be relevant for the sodium
5 channel blockade.

6 This shows the Chiroscience data. This is
7 looking at guinea pig papillary muscles, and action
8 potential parameters measured using standard
9 microelectrode techniques.

10 It shows the effects of bupivacaine and
11 levobupivacaine on V_{max} . V_{max} is the maximum rate of
12 upstroke of the action potential, and reflects the
13 sodium current.

14 Shown here are the effects of the drugs at
15 3 micromolar and 30 micromolar. And the yellow
16 numbers indicate where significant changes compared
17 with pre-drug values occurred.

18 So, bupivacaine at 3 micromolar, which is
19 a significant 14% decrease in V_{max} , indicating sodium
20 channel block.

21 At 30 micromolar, it produced a much
22 larger decrease, a 55% decrease in V_{max} .

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1 Levobupivacaine at 3 micromolar did not
2 produce a significant effect; at 30 micromolar,
3 produced a much smaller effect than was produced by
4 bupivacaine.

5 And as you can see, the between-drug
6 comparisons indicate a statistical significance, and
7 these data clearly show that levobupivacaine is less
8 active on cardiac sodium channels.

9 Now, moving on to look at isolated hearts,
10 whole hearts. And this summarizes data from two
11 studies, one obtained using guinea pig hearts, the
12 other using rabbits. And I would like to point out
13 that these species are appropriate species to use for
14 whole heart perfusion models.

15 I am looking first at the guinea pig.
16 Prolongation of AV conduction. It is found that
17 dexbupivacaine was 54% more toxic than
18 levobupivacaine, and racemate was 30% more toxic than
19 levobupivacaine.

20 QRS duration in the rabbit heart. The QRS
21 duration of the ECG is affected by sodium block, which
22 would tend to prolong the duration. In this, it was

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1 found that the racemate was 229% more toxic than
2 levobupivacaine.

3 I will show you more data from this study.
4 This is the Mazoit Study, using isolated rabbit
5 hearts, and this looks at the effects of
6 levobupivacaine, bupivacaine, and dexbupivacaine on
7 these parameters: the QRS increase, the incidence of
8 atrial ventricular block, and ventricular
9 fibrillation.

10 On the QRS increase, levobupivacaine
11 produced an increase of 59 ms; bupivacaine, an
12 increase of 194 ms; dexbupivacaine, an increase of 236
13 ms. And as you can see, big differences here between
14 these and levobupivacaine.

15 On atrial ventricular block, the incidence
16 with levobupivacaine was 66%, and for bupivacaine and
17 dexbupivacaine, the incidence was higher, at 100% in
18 each case.

19 For fibrillation, no fibrillation occurred
20 in the levobupivacaine-treated hearts; it occurred in
21 66% of the bupivacaine-treated hearts; and 83% of the
22 dexbupivacaine-treated hearts.

1 The important conclusions from this study
2 was that levobupivacaine in comparison with these,
3 produced less prolongation of QRS duration, a lower
4 incidence of atrial ventricular block, and it did not
5 produce ventricular tachycardia, or ventricular
6 fibrillation.

7 Now moving to look at cardiotoxicity in
8 whole animals. And this shows arrhythmia data for the
9 rat and the sheep. And immediately, you can see that
10 there were advantages for levobupivacaine in both
11 studies.

12 I am going to show data from the rat
13 study, and Professor Mather will talk about the sheep
14 data in the next presentation.

15 This is in anesthetized rats. This is the
16 Denson study, looking at the administration of 2 mg/kg
17 intravenously of levobupivacaine and dexbupivacaine.

18 Looking at these parameters, for
19 bradycardia, with levobupivacaine, mild bradycardia
20 occurred in four out of twelve animals; with
21 dexbupivacaine, severe bradycardia occurred in all of
22 the animals.

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1 For Wenckebach rhythms, this is second
2 degree heart block, this occurred in two out of twelve
3 of the levobupivacaine rats, and all of the
4 dexbupivacaine-treated rats.

5 And looking at deaths. This occurred in
6 two of twelve of the levobupivacaine-treated animals;
7 and all of the dexbupivacaine animals.

8 DR. WATCHA: Was that statistically
9 significant?

10 DR. GRISTWOOD: Yes, that was. Okay, now
11 moving on to look at the effects in the anesthetized
12 pig model, and I will make the point here that the
13 pig, like the dog and the sheep, is a widely accepted
14 large animal model to look at local anesthetic-induced
15 cardiovascular toxicity.

16 Here we are looking in anesthetized pigs
17 at QRS prolongation, and ventricular fibrillation in
18 lethal dose.

19 For QRS prolongation, again a clear
20 advantage for levobupivacaine; it was between 25 and
21 47% less cardiotoxic.

22 And on ventricular fibrillation,

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1 levobupivacaine was 58% less cardiotoxic.

2 I am now going to quickly run through the
3 data to substantiate these values. This is the
4 Morrison and Reitz study in anesthetized pigs.

5 The study was carried out in anesthetized
6 pigs, using blinded parallel treatment groups. The
7 drugs were given by coronary artery infusion to avoid
8 effects on the central nervous system complicating
9 interpretation.

10 The drugs were given in 3 mls over 10
11 seconds. In each animal, a dose response was carried
12 out, starting at 0.375 mg, and then increasing the
13 dosage shown, up to the point by which the animals
14 died through ventricular fibrillation.

15 The key measurements were a 12-lead EKG
16 from which PQ, QRS, and QTc intervals were measured.

17 This shows the effects on QRS duration.
18 Here we have the increase in QRS duration in
19 milliseconds, and this is the dose of drug
20 administered. Now, this is shown on a little scale.

21 This is the dose response curve here for
22 bupivacaine, and this is the dose response curve for

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1 levobupivacaine. And you can see the levobupivacaine
2 is to the right of that for bupivacaine, showing that
3 it is less effective in increasing QRS duration.

4 Making comparisons between the drugs at
5 two levels. At the 40 ms increase there was a 25%
6 difference between the two drugs. And at the 90 ms
7 increase, there was a 47% difference between the two
8 drugs.

9 The numbers here indicate the points at
10 which animals died. Back here, there were seven
11 animals in each group. And this shows that for
12 bupivacaine at this point, two animals died.

13 There is an indication that animals died
14 with bupivacaine at lower increases in QRS duration
15 than with levobupivacaine. The suggestion is that the
16 pigs could tolerate larger increases in QRS duration
17 with levobupivacaine than with bupivacaine.

18 This shows the lethality data in greater
19 detail. Here we have the drug injected, the dose
20 injected, and the mean lethal dose with the range.

21 I will take you through one of the
22 bupivacaine animals. This was first of all given

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1 0.375 mg, then 0.75, up to 5 mg, the figure here shown
2 in the white box, which is the point at which the
3 animal died.

4 Looking at bupivacaine, the animals died
5 at 4 mg, 5 mg, and 6 mg, and for levobupivacaine, they
6 died at 7, 8, and 9 mg.

7 There is no overlap here between the doses
8 that cause death in bupivacaine, and those that cause
9 death with levobupivacaine. We had to give more
10 levobupivacaine to produce a death in this model.

11 Looking at the mean lethal doses, for
12 bupivacaine, this was 5 mg; for levobupivacaine, it
13 was 7.9 mg, which is a highly statistically
14 significant difference between these two values,
15 indicating a difference of 58%.

16 Okay, so I have taken you through the
17 Summary Table, and looking at the numbers that are
18 shown here, which relate to relative cardiotoxicity,
19 I believe that this is a powerful, compelling argument
20 that levobupivacaine is less cardiotoxic than racemic
21 bupivacaine, and if you look at the magnitude of the
22 numbers, I believe the body of the data show that we

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1 are hitting the 25% difference between the two drugs,
2 and in many instances, vastly exceeding that value.

3 To summarize, we believe we have a large
4 body of in vitro and in vivo data from a wide range of
5 animal species, which show levobupivacaine to be less
6 cardiotoxic than racemic bupivacaine on cardiac ion
7 channels, EKG variables, arrhythmogenic potential, and
8 lethality.

9 And I would now like to hand over to
10 Professor Mather to talk about the Awake Sheep Model.

11 **Sheep Studies**

12 DR. MATHER: Dr. McCormick, Dr. Horlocker,
13 members of the Committee, ladies and gentlemen, my
14 name is Laurence Mather and I am the Professor of
15 Anesthesia and Analgesia Research at the University of
16 Sidney.

17 I am an independent researcher who has
18 been working on bupivacaine for at least 30 years, and
19 published my first paper on bupivacaine 30 years ago,
20 and I'm still trying.

21 I am interested in -- I'm a
22 pharmacokineticist and much of my approach is that of

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1 a pharmacokineticist interested in anatomical and
2 physiological reality in my pharmacokinetics.

3 In the series of studies I performed over
4 the last five years that were sponsored in my
5 laboratory by Chiroscience and immensely interesting
6 projects, I set out to study the central nervous
7 system toxicity effects of bupivacaine compared to
8 levobupivacaine, notably its convulsant potential.

9 I set out to study the effects on the
10 cardiovascular system, particularly the mechanical and
11 electrical aspects, and also hemodynamic effects, and
12 last but not least, pharmacokinetics.

13 I wanted to know about the dose and blood
14 concentration relationships; I wanted to know about
15 the blood concentration and tissue concentration
16 relationships.

17 I also wanted to put this together and
18 know about the blood concentration and effect
19 relationships.

20 Methods were used comprising two protocols
21 in my laboratory, and one protocol from the laboratory
22 of Dr. Alan Santos from New York. I will describe

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1 them this way.

2 In my laboratory, I set out to study two
3 separate dose ranges of bupivacaine in comparison to
4 levobupivacaine administered in a crossover manner in
5 sheep.

6 A sub-convulsant protocol was chosen in
7 which the dose was administered up to 37.5 mg maximum
8 over one minute.

9 I also compared this to a potentially
10 convulsant, potentially lethal protocol in which doses
11 up to 200 mg were administered over three minutes.

12 The importance of dividing these into sub-
13 convulsant and potentially convulsant protocols is
14 because the act of achieving convulsions causes
15 profound cardiovascular system disturbances, and makes
16 interpretation of the data very muddy, indeed.

17 Because in the first series of up to 200
18 mg of levobupivacaine, we never had a death due to
19 levobupivacaine, I designed what I call the extended
20 dose series in which I used incremental doses of
21 levobupivacaine, starting at the maximum of the
22 previous study; that is, 200 mg, and then incrementing

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1 by 50 mg at a time, until death ensued. I wanted to
2 find out why animals died of levobupivacaine
3 intoxication.

4 In Alan Santos' study, he addressed the
5 question of pregnancy and the old stories that have
6 been circulating now for many years that pregnant
7 animals are more sensitive to local anesthetic
8 intoxication than nonpregnant animals.

9 In his model, he used a repeated
10 intravenous bolus technique, in blinded study with
11 parallel groups of animals, in which the doses were
12 repeated until a lethal outcome ensued, in much the
13 way that this protocol would be the analogy of top-up
14 doses to epidural administration.

15 Basically, the model looks something like
16 this. The chronically cannulated sheep preparation in
17 my laboratories and Alan's laboratories; mine are more
18 sophisticated in terms of the numbers of cannulae and
19 placement of the cannulae than his, but the broad
20 principles are the same.

21 Adult sheep, females, gender, around 50
22 kg; sometimes in Alan's studies they are up to 60 and

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1 sometimes in mine they are as low as 40, but broadly,
2 50 kg animal, in which cannulae are placed into the
3 aorta, pulmonary artery, coronary sinus, sagittal
4 sinus, and the jugular vein.

5 These cannulae are used for obtaining
6 regional blood samples that can be used in mass
7 balance pharmacokinetics calculations.

8 Monitoring cardiac function most
9 sensitively is by placing a pressure-sensitive
10 transducer into the left ventricle, for monitoring the
11 dp/dt .

12 We also place microsonometer probes into
13 the left ventricular free wall, for measuring the
14 shortening of the myocardium during contraction, and
15 also for obtaining an intra-cardiac electrocardiogram
16 signal.

17 We measured hemodynamic effects, cardiac
18 output, left coronary artery, brain blood flow, by
19 sagittal sinus measures, and umbilical artery.

20 In order to achieve this, we use various
21 combinations of transit time probes and doppler
22 probes.

1 We also measure central nervous system
2 excitation by videotaping the whole procedure, and
3 then using a quantitative graded scale; whereas, most
4 researchers would normally use the presence or absence
5 of convulsions as a quantile measure, we have decided
6 to use a graded response measure, and I will explain
7 this more a little bit later on.

8 In some studies, we also measured
9 metabolic characteristics such as oxygen extraction by
10 the heart, and various pharmacokinetics parameters in
11 association with those.

12 Well, to start with, let's look at some
13 results, and the most prominent result from local
14 anesthetic intoxication is that of depression of left
15 ventricular myocardial pressure, dP/dt .

16 It is a common effect of all local
17 anesthetics, and on this slide, I have two pieces of
18 information. I have the time course of the series of
19 doses, and on this side, I have the main decrease of
20 the change in dP/dt .

21 You will see, bupivacaine is the blue,
22 levobupivacaine is the green, and here are the main

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1 values for doses of 12.5, 25, and 37.5 mg.

2 The drug was administered over one minute,
3 the maximum change occurs at around three minutes, and
4 recovery occurs quite quickly for both drugs.

5 Comparing both drugs, you can see there is
6 no difference in the way they depress the myocardium,
7 and this is a common feature for all local anesthetic
8 agents. Indeed, they seem to cause depression in
9 myocardial contractility in roughly the proportion to
10 their local anesthetic potency.

11 Some data showing the next most prominent
12 effect is the convulsant effect of local anesthetics.
13 On this slide, there are two pieces of information.
14 Again, on the left side, you have data from individual
15 animals; on the right side, you have the group mean,
16 and 95% confidence intervals. Bupivacaine, blue;
17 levobupivacaine, green.

18 These are individual animals and the doses
19 at which convulsions ensued. So, this is the frank
20 convulsions quantile response relationship.

21 And there is a separation of the values
22 between bupivacaine and levobupivacaine, such that

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1 when analyzed statistically, there is about a 20% --
2 or rather, a 20 mg advantage in terms of the dose at
3 the onset of convulsions. Levobupivacaine has about
4 a 30% greater convulsant dose to convulsions than does
5 bupivacaine. And so, this is the first clear
6 indication that there is a difference between the
7 drugs.

8 This is now the Central Effects Index.
9 This is really the graded sum of convulsant effects,
10 using a scale which I can explain in more detail,
11 should any Committee member require it.

12 But it looks at the things starting to
13 occur such as twitching -- and this is a lower level
14 score than is arching of the neck, etcetera, until
15 finally, frank convulsions are scored at 100%.

16 Now, these are mean scores for groups of
17 animals as a function of different doses. Again, the
18 green, levobupivacaine and the blue, bupivacaine.

19 At the lowest dose here, levobupivacaine
20 has a much less convulsant potential, much lower
21 score, because essentially it is not convulsant at
22 this dose, whereas bupivacaine is frequently

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1 convulsant at this dose.

2 You see that these are peak effects, and
3 so by the time that the animals are convulsing with
4 larger doses, there is essentially no real difference
5 in the peak effects, but on the right side you see
6 quite marked differences.

7 These low ones here, the 75 mg, represent
8 the convulsant potential, and indeed, the initiation
9 of convulsions, but by the time you get out here, the
10 values for bupivacaine are much larger, because these
11 represent a much longer duration of convulsions.

12 And so, not only is levobupivacaine less
13 likely to cause convulsions; if they do ensue, they
14 are usually of a shorter duration than from
15 bupivacaine.

16 Electrocardiographic effects of course are
17 our greatest concern, and these are two representative
18 cases. This is a case where 200 mg of either
19 bupivacaine or levobupivacaine was infused over three
20 minutes.

21 Here is the baseline electrocardiogram in
22 each case, and there is a strip of which there is the

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1 start of some fairly serious action starting to occur.
2 Let's look at these intentionally.

3 You will see that the electrocardiogram
4 strips may not quite look like what you are normally
5 used to reading as electrocardiogram control strips,
6 because they are intra-cardiac ECGs obtained from the
7 microsonometer crystals.

8 But you see, this is a control level,
9 here. A 3-minute infusion, or 180 seconds, you can
10 see by about 3.5 minutes, there is already the start
11 of quite serious arrhythmias with bupivacaine, of the
12 form of ventricular tachycardia, leading about 30
13 seconds later to ventricular fibrillation, and very
14 shortly after, to death.

15 On the other hand, the same dose of
16 levobupivacaine on a previous occasion in the same
17 animal in fact, produced some widening in QRS, not
18 surprisingly here, but this is about five minutes; at
19 about six minutes, you can see there is bigeminy, but
20 the animal lived to tell the story, that the dose was
21 nonfatal.

22 Now, putting some combined groups of data

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1 together. You have seen single animal cases, now look
2 at some combined data. On the left side, you see the
3 initiation of arrhythmias, and on the right side, you
4 see the sustenance of arrhythmias, as a function of
5 dose. Again, the green is levobupivacaine, the blue
6 is bupivacaine.

7 Within the observation period, at 75 mg
8 doses, neither drug caused significant arrhythmias,
9 but by the time we increased that to 100 mg, four out
10 of six animals demonstrated significant arrhythmias
11 with bupivacaine, none out of six with
12 levobupivacaine.

13 And you can see the dose response curve
14 preceding. The different number of animals are
15 occasioned by deaths occurring in the series, because
16 they were a crossover series, but it is quite clear
17 that the dose response curve for bupivacaine initiates
18 the greater propensity for bupivacaine to induce
19 arrhythmias.

20 And on the right side, you see the
21 duration of the arrhythmias. You see also that those
22 arrhythmias are more sustained than they are with

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1 levobupivacaine.

2 And so, the arrhythmogenic potential for
3 levobupivacaine is this, and the duration of
4 arrhythmias when they occur is this, and the nature of
5 the arrhythmias when they are produced are less
6 malignant than with bupivacaine.

7 Looking together at the fatalities that
8 result from these. Again, two pieces of information;
9 individual animals with 95% confidence intervals.

10 There are two pieces of information for
11 each animal. There is a lower symbol which is joined
12 to a higher symbol.

13 The lower symbol is the dose which was
14 survived, and the higher symbol is the upper dose,
15 which was incremented, and which proved fatal in that
16 animal. They are 50 mg apart.

17 It is clear there is separation between
18 the fatal doses of bupivacaine and levobupivacaine,
19 such that when the group means are observed over on
20 the side, there is about a twofold advantage in favor
21 of levobupivacaine over the racemic bupivacaine.

22 So. indeed, the fatalities due to

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1 ventricular arrhythmias, leading to fibrillation, the
2 propensity for that occurs to a much greater extent
3 with bupivacaine than levobupivacaine.

4 Let's look at some of these so-called
5 extended dose data now. I am going to show you two
6 slides. The first is cardiac output from 250 mg of
7 levobupivacaine, administered over three minutes, and
8 these are individual animal sets of data.

9 You can see, this is 100% of the pre-drug
10 control value, and you can see there is a great deal
11 of variability in response to cardiac output.

12 Sometimes cardiac output is increased
13 markedly. This is a consequence of course of the
14 animal's all convulsing, and indeed, they get
15 autonomic excitation producing a marked increase in
16 cardiac output in these animals.

17 In some animals, cardiac output decreases.
18 But the important point from this slide is, that by
19 the end of the experimental period, they have all
20 returned to near their baseline values.

21 Now, there are no data that are comparable
22 for bupivacaine, because bupivacaine at the same dose

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1 is almost invariably fatal.

2 Some more data from the same set of
3 animals, the same animals, the same color codes. This
4 is the widening of the QRS complex of the
5 electrocardiogram. And you can see, again, there is
6 a marked widening occurring of the QRS complex.

7 But you can also see that these return to
8 essentially baseline values in these animals that
9 survive. And one more time, I repeat, there are no
10 comparable data for bupivacaine, because bupivacaine
11 is usually fatal at this dose.

12 Putting together some pharmacokinetics and
13 some effect data now. On the left side, I have an
14 example from one animal; on the right side, I have
15 group mean data in this cohort of animals.

16 This shows all of the blood concentrations
17 taken from the aortic blood concentrations taken from
18 a range of doses, from 75 up to 200 mg, all plotted as
19 a function of time, a three-minute infusion followed
20 by a fall-away in blood concentration.

21 On these graphs, I have superimposed a
22 green dot for the onset of frank convulsions for

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1 animals receiving levobupivacaine, and a blue dot for
2 those receiving bupivacaine. And again, it is clear
3 that the animals receiving bupivacaine demonstrate
4 their convulsions at lower blood concentrations than
5 those receiving levobupivacaine.

6 There is one green dot out here you may
7 notice; it is from one of the lower doses in fact, in
8 which the onset of convulsions occurred after the peak
9 concentration in arterial blood. And it is one of my
10 philosophies that things like measuring concentration
11 maxima as a way of demonstrating pharmacokinetics
12 interactions is rather a weak technique.

13 And now I have also plotted triangles
14 which demonstrate the end of the convulsive period.
15 When we look at the combined data over on this side,
16 we can see that the time taken to the onset of
17 convulsions, amongst all doses for levobupivacaine, is
18 significantly greater than that for levobupivacaine.

19 When it comes to the time of offset of
20 convulsions, in this cohort, there is no significant
21 difference.

22 Some more pharmacokinetics. This is a

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1 conventional pharmacokinetics analysis that was done
2 for two main reasons. First of all, it was done to
3 demonstrate the differences between the two
4 enantiomers of bupivacaine.

5 And this has long been known -- I amongst
6 others have published this kind of material in the
7 literature over the last ten years -- that if we look
8 at the conventional pharmacokinetics with reference to
9 a two-compartment open model, measured from
10 intravenous administration with arterial blood
11 sampling, and applying all of the usual criteria for
12 kinetic modeling, we see this.

13 The top two are distribution volumes,
14 initial and total distribution. Down here, is
15 internal body clearance and slow half life.

16 It is clear by comparing the red with the
17 green, there is no differences in distribution between
18 the R enantiomer and the S enantiomer of the racemate.

19 It has long been known that the R
20 enantiomer of racemate has a higher total body
21 clearance and a shorter half life than the S
22 enantiomer.

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1 But the important point is that, what I
2 was addressing with these studies, is the other green
3 bar, which is for levobupivacaine administered alone.
4 And there is no significant difference for any
5 parameter in the pharmacokinetics of levobupivacaine
6 administered alone, or as a component of the racemate.
7 That is an important feature.

8 The other important feature that you can't
9 see from this graph is that the data are the combined
10 data set from the trivial 6.25 mg doses, right up to
11 the nearly toxic 200 mg doses. And indeed, there is
12 no significant deviation from these as a function of
13 dose. In other words, there is totally linear
14 pharmacokinetics over this whole range.

15 Some data from Alan Santos to address this
16 question of pregnancy versus nonpregnancy. Alan
17 Santos performed these studies in pregnant animals and
18 nonpregnant animals. And here in this particular
19 graph I have got the accumulated dose to two different
20 endpoints.

21 First of all, the dose to convulsion, and
22 indeed, looking at these data, the first point is,

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1 there are no significant differences between pregnant
2 and nonpregnant animals; however, there are
3 significant differences in the dose of
4 levobupivacaine, which is higher than that of
5 bupivacaine, to the onset of convulsions in both
6 pregnant and nonpregnant animals.

7 When it comes to the dose to circulatory
8 collapse, and the CC:convulsive ratio, no significant
9 differences were found.

10 At the same time, he needed serum
11 concentrations of the drugs, and because serum
12 concentration profiles were non-normally distributed,
13 he reported these as the median and the upper
14 quartiles for each toxic event.

15 In this particular case, the serum
16 concentrations for producing convulsions were not
17 significantly different, but the serum concentrations
18 for producing circulatory collapse were.

19 Indeed, the concentration of
20 levobupivacaine was significantly greater than that of
21 bupivacaine. In other words, there is greater
22 tolerance of levobupivacaine than there is

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1 bupivacaine.

2 Alan is also interested in placental
3 transmission of drugs. The placental transmission,
4 looking at maternal and fetal plasma concentrations at
5 delivery, gives an indication of the relative I guess
6 multifactorial effects that go to regulate this.

7 Many factors, such as plasma binding and
8 blood flow and things like this, go into this
9 equation, but simply using the data as culled sets of
10 data, there is generally observed a large maternal to
11 fetal ratio for bupivacaine. And that ratio for
12 bupivacaine and levobupivacaine is the same.

13 And looking at that ratio down here, the
14 maternal to fetal ratio for levobupivacaine and
15 bupivacaine is not significantly different.

16 In terms of the placental transmission, it
17 can quite clearly be stated that there is placental
18 transmission of levobupivacaine, as there is of
19 bupivacaine, but there is no greater or lesser
20 placental transmission of levobupivacaine, when used
21 alone.

22 Summarizing. I have looked at the central

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1 nervous system toxicity of these agents, Alan did,
2 too, in his studies, and we both came up with the same
3 conclusion. That levobupivacaine has around a 20 to
4 30% advantage in dose-producing convulsions. So,
5 levobupivacaine is less toxic in CNS than is racemic
6 bupivacaine.

7 Cardiac toxicity, the same thing pertains.
8 Levobupivacaine has around a 20 to 30% advantage in
9 dose in the onset of arrhythmogenesis. Certainly,
10 arrhythmias will occur with levobupivacaine, but when
11 they occur, they are of a briefer duration than they
12 are with bupivacaine, and the types of arrhythmias are
13 less malignant than they are with bupivacaine.

14 Fatal doses. Performing the estimated
15 mean and 95% confidence interval, we say that that for
16 bupivacaine has a mean value of around 161 mg,
17 levobupivacaine, 307 mg in the sheep studies.

18 Pregnancy; once and for all, I believe
19 Alan has provided convincing data that there is no
20 effect of pregnancy on either cardiovascular system or
21 central nervous system toxicity of local anesthetic
22 agents, both bupivacaine and levobupivacaine.

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1 Pharmacokinetics, summarizing it. The
2 pharmacokinetics are linear over a very large dose
3 range, and they are not different for levobupivacaine
4 when administered alone, or as a component of the
5 racemic bupivacaine.

6 Thank you. Now, Professor Nimmo is going
7 to speak about clinical human pharmacology.

8 **Human Volunteers**

9 DR. NIMMO: Dr. McCormick, Dr. Horlocker,
10 ladies and gentlemen, good morning. I hope that my
11 Scottish accent will not be too difficult for you to
12 follow.

13 My name is Walter Nimmo. I'm the Chief
14 Executive of Inveresk Research, a contract research
15 organization working with Chiroscience.

16 I would like to present a link between the
17 preclinical data you have just seen, and the clinical
18 trial data you are about to see, by describing the
19 comparison of effects of levobupivacaine and
20 bupivacaine on the heart in two healthy volunteer
21 studies.

22 The studies will be known to you by the

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1 numbers 004801, as a comparison of the cardiovascular
2 effects of levobupivacaine and bupivacaine following
3 intravenous administration; and 012105, as a
4 comparison of the effects of levobupivacaine and
5 bupivacaine on QT dispersion, EKG, and the signal
6 averaged EKG.

7 Study 004801 was the first administration
8 to man of levobupivacaine intravenously. In 14
9 healthy male volunteers, a lidocaine pretest was
10 conducted; lidocaine was infused until the volunteers
11 all experienced CNS side effects, such as tingling of
12 the tongue, circular molar analgesia, or
13 lightheadedness.

14 Approximately one week later, they entered
15 a double-blind, randomized, crossover study and all
16 volunteers received levobupivacaine and bupivacaine
17 one week apart.

18 The drug was given by IV infusion at a
19 rate of 10 mg/minute until there was evidence of CNS
20 symptoms, similar to what they had experienced with
21 the lidocaine.

22 In this study, a variety of tolerability

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1 observations were made; pulse rate, blood pressure,
2 EKG, and continuous monitoring of the EKG, and in
3 addition as a monitor for safety, we measured cardiac
4 index and other variables using the BoMed thoracic
5 impedance apparatus.

6 This machine presents on screen the
7 average of the previous 16 beats, and the equipment is
8 registered as a regulatory Class II by the FDA.

9 We monitored cardiac index, stroke index,
10 ejection fraction, and acceleration index. Your
11 reviewer, Dr. DiMarco, says that these observations
12 are not blood-independent and that is true, but the
13 acceleration index attempts to do this by measuring
14 the initial acceleration of blood in the left
15 ventricle in the first 10 to 20 milliseconds after the
16 aortic valve opens.

17 These are the dosing details from this
18 study, and the doses of drugs administered did not
19 differ significantly. For levobupivacaine, the mean
20 dose was 56 mg and for bupivacaine, the mean dose was
21 47.9 mg.

22 The dose range you see was 17.5 to 150 mg

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1 for levobupivacaine, and only in this group did any
2 volunteer achieve the maximum dose allowed, which was
3 150 mg, without CNS effects.

4 The bupivacaine range was 22.5 to 110 mg.
5 The mean maximum concentration was achieved at the end
6 of the infusion and did not differ significantly
7 between the two groups, it was 2.62 micrograms/ml for
8 levobupivacaine, and 2.25 micrograms/ml for
9 bupivacaine.

10 This slide, ladies and gentlemen, shows
11 the statistically significant cardiac contractility
12 results. You see data for stroke index in ml/m².
13 Acceleration index per second/per second, and the
14 ejection fraction as a percentage.

15 And you see the mean change at the end of
16 the infusion for bupivacaine and for levobupivacaine,
17 and the p-value.

18 Notice that in the bupivacaine group,
19 there was an average change of almost 11 mm/m²,
20 between the beginning and the end of infusion, and
21 only 3.3 mls/m² in the levobupivacaine group, and this
22 was a highly significant difference, and greater than

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1 25% was requested.

2 For the acceleration index, the change
3 from pre-dose to the end of infusion was .18 per
4 second per second, and in the levobupivacaine group,
5 it was .06 per second per second. This also achieved
6 significant difference.

7 In the ejection fraction, there was a
8 significant fall from pre-dose in both groups, but the
9 difference between the groups was not significantly
10 different.

11 These data are shown graphically on this
12 slide, as a percentage fall. In the bupivacaine group
13 for stroke index there was an average, almost a 20%
14 fall in stroke index, compared with a 7% fall for
15 levobupivacaine.

16 For the acceleration index, you see the
17 data, almost 40% fall from beginning to end of
18 infusion, compared with just under a 5% fall for
19 acceleration index.

20 In the 12-lead EKGs, this slide shows the
21 only significant differences achieved. For the PR
22 interval, there was a significant increase from pre-

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1 dose in the bupivacaine group, from 165 msec on
2 average, there was an increase of 11 msec, which just,
3 just achieved significant difference.

4 And in the levobupivacaine group, there
5 was no significant increase from pre-dose, 165 on
6 average before infusion, and increased by an average
7 of 5 msec. This was not significantly different, but
8 there was no significant differences between the
9 groups.

10 In the QTc interval, measured in these
11 Hewlett-Packard EKGs, once again there was a
12 significant increase in the bupivacaine group. It
13 just achieved significant difference with an average
14 increase of 22 msec from a baseline of 384.

15 And in the levobupivacaine group, there
16 was no significant increase, it just failed to achieve
17 significant difference, 21 on average, increasing on
18 a baseline of 388.

19 And once again, there was no significant
20 difference between the two groups.

21 So, the conclusion from this first
22 administration to man study was that levobupivacaine

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1 has less effect on cardiac contractility measures than
2 bupivacaine, and there was no between treatment
3 differences seen in the EKG intervals.

4 We went on to study another human
5 volunteer study in an attempt to review more in-depth
6 the EKGs. On this occasion, 22 healthy volunteers
7 were entered into the study, and completed the study.

8 Once again, all 22 received a lidocaine
9 pretest to identify CNS symptoms in all the
10 volunteers.

11 On this occasion, all 22 volunteers
12 received bupivacaine at an infusion rate of 10 mg per
13 minute, until they achieved the same side effects.
14 And the dose range was 30 to 120 mg.

15 The 22 volunteers were then randomized to
16 a double-blind, parallel group to receive
17 levobupivacaine or bupivacaine, 11 in each group, and
18 this randomization was stratified according to dose.

19 Observations that were made, apart from
20 safety observations, included the 12-lead EKG, QT
21 dispersion, and signal averaged EKG, using a
22 Marquette.

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1 The data from this study are shown on this
2 slide. On the top of half of the slide you see the
3 doses that were given. Once again, there was no
4 significant difference in the mean dose administered
5 between levobupivacaine and bupivacaine.

6 The dose range was 40 to 110 mg for
7 levobupivacaine, and 30 to 120 mg for bupivacaine.

8 The mean Cmax was very similar to the
9 previous study, 2.75 micrograms/ml for
10 levobupivacaine, and 2.44 micrograms/ml Cmax in the
11 bupivacaine group.

12 The only significant difference found in
13 this study was in the QTc interval in volunteers who
14 had received more than 75 mg of drug.

15 In the bupivacaine group, there was a
16 significant increase in QTc, which was of 24 ms on
17 average, compared with 3 ms in the levobupivacaine
18 group. This was a significant observation.

19 In conclusion, from this study, at doses
20 greater than 75 mg intravenously in healthy
21 volunteers, bupivacaine produced a significantly
22 greater QTc increase than levobupivacaine.

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1 No other significant differences in
2 effects on the EKG were detected.

3 And the conclusion from both studies,
4 levobupivacaine has less effect on cardiac
5 contractility measures than bupivacaine.
6 Levobupivacaine in doses greater than 75 mg has less
7 effect on QTc than bupivacaine.

8 We believe that this concurs with the
9 preclinical evidence you have already seen, which
10 shows that, compared with bupivacaine, levobupivacaine
11 is associated with a lower binding affinity to human
12 cardiac potassium channels, and significantly greater
13 doses are required to prolong QTc in the pig.

14 Thank you very much. I would like to hand
15 over to Dan Kopacz, who will present some clinical
16 efficacy data.

17 Clinical Trial Experience

18 DR. KOPACZ: Good morning, ladies and
19 gentlemen. My name is Dan Kopacz. I'm a staff
20 anesthesiologist at the Mason Clinic in Seattle.

21 I have been asked to address the efficacy
22 of levobupivacaine in the trials that have been

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1 performed, comparing it to bupivacaine, as used in the
2 operating suite or in the obstetrics suite for
3 Cesarean Section.

4 I will cover four studies; they are all
5 epidural studies. They are all double-blind,
6 randomized, parallel group studies, with bupivacaine
7 as the comparison drug.

8 The first two studies are in Cesarean
9 Section, the methods of which are combined actually on
10 this slide, because they are quite similar.

11 The differences are, one study is 25 mls
12 of study drug, or racemic bupivacaine, the other study
13 used a total of 30 mls.

14 Both studies used 0.5% study drug.

15 The standard for obstetrics, a lumbar
16 epidural was placed in the left uterine displacement
17 position. Drug was injected through a catheter after
18 a test dose, which included epinephrine in one study;
19 that was a lidocaine test dose. In the other study,
20 it was a study drug containing test dose.

21 What I hope to show on going through these
22 four studies are that, from a clinical perspective,

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1 these drugs are very similar and actually
2 indistinguishable, but there are some minor
3 differences, and where these appear, I will point them
4 out, but I think you will see that the differences
5 relative to the similarities are relatively small.

6 This is the first obstetrics study.
7 Again, comparing 0.5% levobupivacaine on the left,
8 0.5% racemic on the right, which will be the standard
9 convention.

10 Just to go through the schema of this
11 slide, because you will see it again in the other
12 studies as well, the onset data for both drugs will be
13 on the outside slide; the regression data will be on
14 the inside of the slide; and the endpoints will be on
15 this dermatome man, if you will.

16 So what you see here is an onset to T5,
17 which was the predetermined primary efficacy point in
18 this study, of about ten minutes for levobupivacaine,
19 and six minutes for racemic bupivacaine.

20 This was statistically different, and I
21 will explain more about that in a second, and you see
22 no difference in any of the regression data, with the

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1 exception that levobupivacaine takes a little longer
2 to regress and you will see that again, as a trend,
3 that in only one instance is that statistically
4 significant.

5 These are two patients that were excluded
6 from that trial because they didn't reach the T5 block
7 height. One patient reached T6, which actually
8 occurred at 15 minutes.

9 The default mechanism for someone who
10 didn't reach a T5 block height, was to use the time of
11 start of surgical incision, or the start of the C
12 Section as the onset time. This patient's C Section
13 got started at 40 minutes.

14 The second patient had a block of T12 at
15 ten minutes; that was clearly going to be inadequate.
16 They rolled this lady back up and did a spinal
17 anesthetic, and the surgical procedure started 29
18 minutes after end of drug injection.

19 So, these two patients had onset times of
20 40 and 29 minutes, which was included in that onset
21 time from the previous slide, which somewhat skews the
22 results. And if you remove these two patients, which

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1 is not a statistically nice thing to do, the onset
2 time drops to eight minutes, and the difference
3 between those two drugs disappears.

4 I will also point out that that is the
5 only place in any of the studies I will go over, and
6 any of the studies actually that were done clinically,
7 where there was a difference in onset time.

8 Various muscle relaxation measures were
9 also made in these studies. For the Cesarean Section
10 studies, a simple scale, four-point scale, actually,
11 there is a grading of poor, fair, good, and best for
12 the abdominal muscles, where it was rated by both the
13 obstetrician, as is shown in this slide, and the
14 anesthesiologist.

15 I think you can see quite clearly that
16 these drugs work the same, with the vast majority of
17 patients having neither good nor best conditions for
18 the C Section.

19 This data is identical for the
20 anesthesiologist, or quite similar, I should say, to
21 the anesthesiologist, not only in this study, but in
22 the next study, which is the other Cesarean Section

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1 study.

2 Patients also rated their pain during
3 their C Section at five different time points. What
4 you see on the left is a truncated VAS pain scale,
5 where 0 is no pain whatsoever; 10 is the highest pain,
6 which is off on the ceiling.

7 They rated pain at skin incision;
8 abdominal opening, the musculature; uterine incision;
9 uterine manipulation, after the baby was delivered;
10 and in the recovery room.

11 Now, the protocol stated that all of these
12 time points should be added together and a comparison
13 be made on the sum of all of these time points. And
14 there was no statistical difference when you did that,
15 not only in this study, but in the next study as well.

16 But there is some suggestion there may be
17 a difference at the time of uterine manipulation with
18 significantly more pain with the bupivacaine group.
19 However, when you look at the same data from the
20 second study, this peak is in existence, so it's just
21 isolated to this study.

22 This is that second Cesarean Section study

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1 data, again, comparing 0.5 to 0.5, onset similar to
2 the last study. It takes a little bit longer because
3 this study had the lesser of the two drug amounts, 25
4 ccs relative to 30 in the first one.

5 But again, ten minutes versus nine
6 minutes. Again, not different in this study. And
7 regressions to T10 at about five hours, and about
8 eight hours for complete regression of blockade. Once
9 again, a little bit longer it appears with
10 levobupivacaine, but no statistical significance.

11 Motor blockade of the lower extremities
12 was measured by a standard Bromage scale in both of
13 these studies as well. Not really clinically
14 relevant, because they are having abdominal
15 procedures, but just to go through the scale briefly.

16 Zero is no lower extremity muscle blockade
17 whatsoever. The other extreme is a completely flaccid
18 lower extremity at grade three.

19 In this second study, there was
20 statistical significance in that fewer of the patients
21 -- I should say, more of the patients in the
22 levobupivacaine groups tended to have less motor

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1 blockade using this Bromage scale, relative to
2 bupivacaine.

3 This same measurement was also made in the
4 first study, and this propensity of levobupivacaine to
5 produce less motor blockade wasn't apparent in the
6 first study. So you have, again, one study saying one
7 thing and one saying slightly different.

8 The protocol also stated that patients
9 that had no lower motor blockade whatsoever should be
10 excluded from measurements of offset of motor
11 blockade, so that these patients are excluded when you
12 measure the time that motor blockade resolves.

13 There is statistical significance and it
14 appears that levobupivacaine produces a longer
15 duration of motor blockade; but again, that is only in
16 the patients that got any degree of motor blockade
17 whatsoever. That difference also wasn't apparent in
18 the first C Section study.

19 To summarize the C Section studies, both
20 drugs produce adequate anesthetic for the intended
21 procedure. There tended to be shorter onset with
22 levobupivacaine in one study, statistically; I'm not

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1 sure it was clinical significant, but there tended to
2 be a little less motor block in the other study.
3 Again, I am not sure that is clinically significant,
4 either.

5 The third epidural study is shown here.
6 This now is a three-group study in surgical patients
7 having lower limb vascular surgery. Again, the 0.5 to
8 0.5 comparison, now with the third group added in,
9 being 0.75% levobupivacaine.

10 The other difference in this study,
11 relative to the obstetrics study, is that now it is a
12 smaller dose, 15 ml total, as opposed to 25 to 30 in
13 the Cesarean Section study patients.

14 These are the results from this study.
15 Onset time again shown on the outside. This is first
16 appearance of anesthesia, which is not clinically
17 relevant whatsoever.

18 Peak block height of T7 versus T8. Onset
19 time of 15 to 20 minutes, no differences there.
20 Again, regression at about four hours to T10, complete
21 regression, six to seven hours. No differences in any
22 of these parameters.

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1 What is also shown on this slide is, not
2 only the mean peak block height of T7 and T8, but also
3 the range of peak block height. One patient in the
4 0.5% bupivacaine only got a peak block height of L2,
5 with 15 ccs. The lowest peak block height was T12
6 with levobupivacaine, and one patient had a T6 for the
7 racemic bupivacaine. Not statistically different, but
8 gives you more of a clinical feel for how this drug is
9 going to behave.

10 The data on the left side are identical to
11 the last slide. The data on the right side is what's
12 new; that's the 0.75%, the third group in this study
13 now.

14 The only significant difference in this
15 group, relative to either of the other two groups is
16 the total duration of sensory blockade. There is no
17 difference in onset, regression to T10, but as you
18 would expect, as you give 50% more drug, same volume,
19 higher concentration, you now have a total duration of
20 about eight hours.

21 Using that same Bromage scale that I
22 talked about in the second obstetrics study, motor

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1 blockade was also assessed, with a Bromage scale in
2 this study, grades zero, one, two, and three.

3 When you compare the three groups, it
4 tended to be a significant difference, but it didn't
5 reach statistical significance, and what you see from
6 looking at that graph, grossly, is the 0.5%
7 levobupivacaine tended to produce less motor blockade.

8 As you would expect, the 0.75% group
9 tended to produce a little heavier motor blockade, and
10 the racemic group was intermediate between the two.

11 Therefore, as you would likewise expect
12 with using a higher dose, you get a little bit greater
13 degree. It takes a little longer to get that greater
14 degree of motor blockade with the 0.75%, and it
15 likewise lasts a little bit longer, but likewise,
16 compared to the top, there is no real statistical
17 difference between these drugs.

18 The final study is my favorite, because I
19 was the principal investigator. It compares 0.75%
20 levobupivacaine, 0.75% bupivacaine in patients having
21 lower abdominal surgery, 56 patients, equally
22 distributed between the groups.

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1 The protocol also had provision that
2 during surgery, if the patient needed or if the
3 investigator felt that the patient needed more
4 blockade, they could get a top-up of 7ccs.

5 One patient in the levobupivacaine group,
6 and two patients in the racemic bupivacaine group got
7 top-ups. Those patients obviously are excluded from
8 the data that I will show in the next slide, and in
9 addition, one patient in the racemic bupivacaine group
10 only got an L1 block with 20 ccs of 0.75% bupivacaine.
11 That patient likewise is excluded.

12 And here are the data. There was a
13 difference in primary endpoint in this study. The
14 primary endpoint was actually onset of sensory
15 anesthesia to T10, which was the lowest level which we
16 felt we could initiate the surgical procedure. That
17 is the intermediate number and onset, 14 minutes,
18 onset to T10.

19 Peak onset to 25 to 30 minutes; a little
20 bit higher than the previous slide, because we are
21 giving a bigger dose-up, obviously, but T5, again
22 similar ranges. This is that one patient that was

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1 excluded.

2 Regression now is two segments, T10 and
3 complete regression. Five hours, six hours, and nine
4 to ten hours. And this is one point where there is
5 actually statistically significant difference between
6 the two drugs, with the longer duration, 45 minutes
7 longer with 0.75 levobupivacaine.

8 But I would suggest to you, after eight or
9 nine hours, a difference of 45 minutes really isn't
10 clinically significant, in my opinion.

11 The other test that was done in this last
12 study was another abdominal muscle test, that being
13 the RAM test, which stands for rectus abdominous
14 muscle.

15 Basically, what you had to do is make the
16 patient do a sit-up with their arms behind their head.
17 If they can do that, it's a grade zero -- I'm not sure
18 everyone can do that, but --

19 A grade one, you have to fling your arms
20 in front of you to do the sit-up, and as your muscles
21 get more and more relaxed, you are less able to do a
22 sit-up, so you get a grade two, grade three, grade

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1 four, and grade five. Grade five, you basically can't
2 even more your shoulders off of the table.

3 For abdominal surgery, you need a grade
4 three to have enough relaxation of the muscles for the
5 surgeon to operate.

6 And you can see here, by and large, 90% of
7 the patients got grade three at 30 minutes. And the
8 muscle relaxation was adequate without any other
9 intravenous muscle relaxants to perform the operation.
10 No difference, again, between the two drugs.

11 There are also a number of other clinical
12 studies that compare bupivacaine and levobupivacaine.
13 By and large, they all show no difference,
14 statistically, or clinically. One of those was a
15 supraclavicular block and brachial plexus. There were
16 two ophthalmologic blocks comparing peri-bulbar
17 anesthesia.

18 There are infiltration studies, two of
19 them, for patients having hernia operation under
20 straight infiltration analgesia. And also labor
21 analgesia patients and other obstetric patients. All
22 of this data is available, so if anyone has any

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1 questions about it, feel free to ask about it.

2 By and large, again, they show that both
3 drugs are effective, clinically, and that there are
4 very little difference between them.

5 In conclusion, the points that I basically
6 wanted to get across are, both drugs are very
7 effective local anesthetics when given at equal
8 concentrations, equal volumes, and therefore, equal
9 doses, for the various regional block that we perform
10 in surgery.

11 There are some minor differences, but by
12 and large, those differences are not very obvious,
13 relative to the similarities.

14 There may be some slight differences at
15 onset as shown in the first study. There may be some
16 differences in duration, as has been shown in most of
17 these studies, but only statistically in the last, as
18 well as some differences in motor blockade as shown in
19 some of the four studies that I reviewed.

20 Now, I would like to pass the microphone
21 to Dr. Jim Crews, who is going to review the safety
22 data from the clinical program.

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1 free EEG epochs were taken from each significant time
2 point during the observation period, and submitted for
3 power spectrum analysis.

4 I won't go into a lot of detail on this.
5 It was, as you might imagine, a very complicated study
6 and the amount of data that was produced from this
7 study is impressive in terms of its volume, but
8 basically, the conclusions that can be drawn here was
9 that, bupivacaine showed a slowing of the EEG, which
10 is consistent with the CNS depressant effect that you
11 might expect with any CNS depressant type drug.

12 Levobupivacaine produced a similar CNS
13 depressant effect, but the effect was less in terms of
14 both the magnitude of the CNS depression, as well as
15 the extent, or the areas of the brain involved in EEG
16 changes, representative of CNS depression.

17 More adverse events were reported by the
18 subjects during the bupivacaine infusion than by the
19 same subjects during the infusion of levobupivacaine,
20 including an increase in blood pressure during the
21 bupivacaine infusion which was not seen during the
22 levobupivacaine infusion.

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1 This just shows the plasma concentrations
2 obtained in the patients with normal renal function.
3 On this axis you see the values expressed in mg/l or
4 micrograms per ml, with most patients having peak
5 plasma concentrations in the range of 1 to 2
6 micrograms/ml. A couple of patients up around 2, and
7 one patient at 3.7.

8 Twenty-six of the twenty-eight patients
9 had adequate surgical anesthesia within 30 minutes of
10 performing the block, which was the cutoff time set in
11 study.

12 The two patients who did not have adequate
13 surgical anesthesia within the 30 minutes both had a
14 complete block, postoperatively.

15 No hemodynamic or CNS changes suggestive
16 of either cardiovascular or CNS toxicity were noted in
17 any of the patients, including the patient who got the
18 highest peak plasma concentrations.

19 The average maximum concentration obtained
20 in the study was 1.58 micrograms/ml, and the time to
21 that maximum level was 39.5 minutes.

22 So, what we can conclude from this, in the

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1 cases of the single highest doses of the drug, in the
2 range of 250 to 300 mg for brachial plexus block, that
3 this dose is well-tolerated without any signs of
4 cardiovascular or CNS toxicity.

5 Looking at the maximum dose of
6 levobupivacaine administered cumulatively over a 24-
7 hour period, we can look toward the four clinical
8 trials where levobupivacaine was administered for
9 continuous postoperative analgesia, following the use
10 of levobupivacaine for surgical anesthesia for the
11 surgical procedure.

12 There were 326 patients in these four
13 clinical trials. No patients demonstrated any signs
14 or symptoms of either cardiovascular or CNS toxicity
15 related to the cumulative dosing during the 24 hour
16 study period.

17 This just shows a breakdown of the types
18 of doses that were received. Six of the patients out
19 of the 326 received 24 hour cumulative doses exceeding
20 600 mg.

21 Another eight patients received doses in
22 the 500 mg range; 45 patients received doses,

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1 cumulative doses, in the 400 mg range, and then the
2 remainder of the patients received doses in the 250 to
3 400 mg range, in the cumulative dose over 24 hours.

4 There were three cases of investigator-
5 suspected intravascular injections, which occurred
6 during the phase II and phase III studies. This
7 involved a total of over 1350 patients; 879 of these
8 patients received levobupivacaine, the remainder of
9 the patients received racemic bupivacaine.

10 And out of the total of the 1355 patients,
11 there were three suspected cases, when the blinding
12 was broken, two of these patients had received racemic
13 bupivacaine, and only one patient had received
14 levobupivacaine.

15 Looking at the response that patients had
16 in these cases of suspected intravascular injection,
17 the first patient we will discuss was from one of the
18 C Section trials where the patient received epidural
19 bupivacaine, 0.5%, a dose of 120 mg.

20 The patient exhibited slurred speech,
21 became unresponsive, bradycardic, hypotensive, and had
22 transient uterine hypertonia.

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1 studies, where the patient received a dose of 142.5 mg
2 of levobupivacaine 0.75%.

3 This was administered via an epidural
4 catheter, following a negative test dose for
5 intravascular injection.

6 The patient became drowsy, had slurred
7 speech, and a period of excitation where she had some
8 screaming, which was self-limited, exhibited at no
9 time any changes in cardiovascular status, and did
10 receive two doses of IV thiopental which were said to
11 be for convulsant prophylaxis.

12 This is the only pharmacokinetics profile
13 that we have from the intravascular, suspected
14 intravascular injections. Again, this occurred with
15 bupivacaine, not levobupivacaine.

16 And you can see from the data, this was
17 from the supraclavicular block study, the patient
18 receiving intravascular injection had a observed peak
19 plasma concentration of greater than 5 micrograms/ml,
20 with the remainder of the patients having peak plasma
21 concentrations in the 1 microgram/ml range.

22 So, from the information that we have

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1 seen, both from the clinical data, as well as the
2 preclinical data, there does seem to be an equivalent
3 clinical effect for levobupivacaine as compared to
4 bupivacaine, and a greater margin of CNS and
5 cardiovascular safety in the event of an unintentional
6 overdose or intravascular injection.

7 I meant to mention this in the beginning,
8 but on the Agenda it says that I would be discussing
9 cases of overdose. There were no cases of overdose of
10 local anesthetic in the clinical development program,
11 but the overdose term on the Agenda refers to these
12 cases of unintentional intravascular injection.

13 Thank you.

14 DR. GENNERY: Thank you very much, Dr.
15 Crews. Before I just finally wrap-up, I would like to
16 draw the Committee's attention to the Briefing
17 Document that we provided to you, where we noted that,
18 having supplied Dr. Raymond Woosley of Georgetown
19 University Hospital, all the original data on 012105,
20 he had actually come to a different conclusion in
21 terms of the outcome of the electrocardiographic
22 analysis.

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1 And fortunately, Dr. Woosley has been able
2 to join us here today, and before I wrap up, I would
3 just like to give him the opportunity of explaining
4 where he sees these differences lay.

5 **Electrocardiographic Analysis**

6 DR. WOOSLEY: Thank you, Brian. I don't
7 have any slides, but I think your document does have
8 the graphs that I will refer to.

9 Chiroscience asked me to be a consultant
10 on this project sometime ago, and to look at the
11 electrocardiographic data that they had available, and
12 the preclinical pharmacology on the isomers, probably
13 because of my previous interest in differences in
14 sodium channel blockade the myocardium, so it was
15 something of interest to me, and it was an interesting
16 challenge.

17 When I looked at the pre-clinical
18 pharmacology data, Study 012105 had subset analysis
19 that indicated that there might be a trend toward a
20 difference in the QT data, so I suggested that there
21 may be some confounding variables in this.

22 The two that I thought might be playing a

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1 role were, one, a change in heart rate, which could
2 certainly change the Bizette-corrected QT interval,
3 and then the second was the fact that the data that
4 they had obtained was using the Marquette System.

5 And we have published an abstract -- we
6 don't have a final publication out, but -- of a
7 comparison of the Marquette and the Hewlett-Packard
8 automated systems to what we and many other people
9 use, which is more manual, a bit pad method for
10 comparing the QT interval -- for analyzing the QT
11 intervals.

12 We analyzed the QT intervals and the QRS
13 data in that study, and found that there were, as we
14 had seen before, major discrepancies between our
15 measurement and the machine measurement. And in the
16 document, you will see the comparison of those.

17 There were some differences due to the
18 change in heart rate that was seen in that study, but
19 the major differences were caused by a general under-
20 reading of the QT interval by the Marquette, compared
21 to our data.

22 So, when we did the analysis, you will see

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1 that we felt that there was no difference in the QT in
2 the two data sets.

3 My conclusion at the end of that, as you
4 will see in my report, was that this study indicated
5 the maximum ethical attempt to administer this drug to
6 normal volunteers, to examine potential differences in
7 the electrocardiogram, and I didn't see that there
8 were any statistically significant changes in the QT
9 interval.

10 And then, putting that in -- adding to
11 that, the preclinical pharmacology data, I felt that
12 they had demonstrated in the preclinical data that
13 there was a significant pharmacologic difference in so
14 many models, but that it would be unethical to take
15 normal volunteer studies to anything, any further
16 point.

17 And that, the maximum tolerated dose that
18 they had been able to administer to normal volunteers
19 was inadequate to produce any changes in the QT
20 interval, and therefore, unlikely that they would be
21 able to show any differences between the QT with the
22 L isomer compared to the racemate.

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1 So, if there are questions about the data
2 that I have presented, I would be glad to answer
3 those, but those were my general conclusions.

4 **Concluding Remarks**

5 DR. GENNERY: Thank you. Thanks, Ray. If
6 I could just take the opportunity then of summing up.
7 We believe that we have managed to show a clear
8 difference between the cardiovascular toxicity seen
9 with levobupivacaine and bupivacaine, in all the
10 preclinical models that were tested, and that these
11 all well exceed the 25% that we discussed two years
12 ago.

13 That in clinical pharmacology studies we
14 have seen differences, including those in the central
15 nervous system, between levobupivacaine and
16 bupivacaine.

17 And finally, the meta analysis of the
18 studies that was presented by Dr. Crews showed that
19 small differences can be seen, even when the drugs are
20 being compare in normal use. And this is perhaps a
21 somewhat unexpected finding.

22 We believe that these differences are

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1 relevant, in that levobupivacaine has been shown to
2 have the same efficacy as bupivacaine when used at the
3 same concentrations and volumes, in a wide variety of
4 applications, including epidural use in surgery, and
5 Cesarean Section, and peripheral blocks.

6 What I have tried to do here is to tie
7 everything together, and see how the story sort of
8 comes together.

9 In specific observations, the implication
10 of those observations and how that may translate into
11 a clinical situation in the event of an unintentional
12 overdose.

13 So, looking first at the cardiac sodium
14 channel effects being less with levobupivacaine. That
15 is the, that will translate into a lesser prolongation
16 of QRS, and we have seen that in the pharmacology
17 studies that we have presented to you, implying a
18 lower risk of ventricular arrhythmias, particularly
19 tachyarrhythmias in the event of an unintentional
20 overdose.

21 Less effect on potassium channels, which
22 translate into less prolongation of QT and QTc.

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1 Again, we have seen that in some of the pharmacology
2 models, lower risk of Toursade des pointes.

3 And then we are seeing less prolongation
4 of PR interval, suggestive of less effect on calcium
5 channels, with a lower risk of reentry arrhythmias or
6 of complete heart block.

7 We believe that we have addressed the
8 questions posed by the Agency to the Advisory
9 Committee and we have shown that levobupivacaine is a
10 quantitatively different drug to bupivacaine,
11 particularly in respect to its cardiovascular and
12 central nervous system side effects, and the PI should
13 therefore not contain a boxed warning. And that the
14 safe and effective use of levobupivacaine can be
15 ensured by appropriate wording in the labeling.

16 Thank you.

17 **Questions From the Committee**

18 DR. HORLOCKER: Could we have the lights
19 up, please? We will now entertain questions from the
20 Committee. I would like to start out. I have two
21 questions, one on clinical and one on the laboratory
22 studies that have been done.

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1 First of all, some of the striking
2 characteristics of the bupivacaine-induced toxicity
3 was that the CV toxicity occurred without prior CNS
4 toxicity. And then secondly, the parturients were
5 very difficult to resuscitate.

6 In any of your laboratory studies, did the
7 animals in either the bupivacaine or the
8 levobupivacaine groups demonstrate a CV toxicity,
9 prior to the CNS toxicity, or did that always have the
10 excitatory, seizure-type disorder first.

11 And then secondly, do we have any data on
12 the resuscitation of these animals? Are they more
13 easily resuscitated when they receive levobupivacaine?

14 And my second question concerning the
15 clinical studies is that, certainly you have
16 demonstrated that there is a decreased magnitude and
17 shorter duration of the CV and CNS effects, but do
18 they occur at similar levels, similar timing, or is it
19 just that they occur at the same time, but they are of
20 less magnitude?

21 DR. GENNERLY: I wonder if I could ask Dr.
22 Mather to address the first issue?

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1 DR. MATHER: Dr. Horlocker, the course of
2 the events is fairly predictable. There is always a
3 CNS effect.

4 Now, we use a three-minute period of
5 infusion intentionally to clarify this. We want to
6 see things happening. And we can always see the
7 prodrome of convulsions in our experimental animals
8 and certainly subclinical toxicity of course is
9 attendant, for example, changes in left ventricular
10 dP/dt and left ventricular and diastolic pressure
11 increases.

12 They are occurring all of the time without
13 any overt CNS symptoms, but the serious CNS symptoms
14 to which you refer, in our experience, are never
15 without a preceding CNS syndrome.

16 DR. HORLOCKER: Are there any other
17 resuscitation data available on these animals?

18 DR. GENNERY: Yes, sure. Thanks very
19 much. One of the protocols that we agreed to do was
20 one in dog resuscitation, and the experimental phase
21 of that is finished.

22 Dr. Feldman, who is the investigator, has

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1 come with us, and he has a little bit of preliminary
2 data to show on that, if I could ask him to come to
3 the microphone.

4 DR. FELDMAN: These experiments, I just
5 wanted to stress that this data is extremely
6 preliminary. We just finished these studies about two
7 weeks ago.

8 We did a cursory examination to look at
9 some very specific points, which we felt were the most
10 critical points probably of the Study, just to be able
11 to present some of this preliminary data to the
12 Committee.

13 These experiments, just to give you a
14 brief outline of what they were, we had an in a series
15 of experiments prior to this, determined the
16 convulsive dose in the dog by intravenous infusions,
17 2 mg/kg/minute of levobupivacaine, bupivacaine, and
18 robivacaine.

19 We used those convulsive doses in this
20 study. In this study, the convulsive dose was
21 administered over 30 to 40 seconds, intravenously.
22 Resuscitation was begun 30 seconds after the onset of

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1 seizure activity.

2 And the resuscitation basically consisted
3 of we would treat whatever toxicity happened to be
4 most life-threatening at the time.

5 If seizures were the only form of toxicity
6 which were occurring, then we treated them with
7 barbiturates, intubation, and oxygen ventilation.

8 We treated arrhythmias, ventricular
9 arrhythmias, with Bertyllium. Hypotension was either
10 treated with amranone; we used atropine and
11 phenylephrine if necessary. In the worst cases, we
12 had reverted to chest compressions and DC
13 cardioversion.

14 So, this slide represents the first
15 portion of the study, which is the convulsive dose,
16 given as I said over about 40 seconds, intravenously.

17 We haven't broken the code on these
18 experiments yet, so we have assigned them just a drug
19 code, D, E, and F, so that we were able to group them
20 to see what was going on in the different groups.

21 Because the data has not been analyzed, we
22 would prefer not to break the code until we have

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1 completely analyzed it.

2 I should also point out that incidents of
3 AV block and incidents of ventricular arrhythmias are
4 rather broad in this definition, meaning that if we
5 had two incidents of AV block in a particular animal,
6 it is listed here. If we had one PVC, it's listed
7 here.

8 If we had a burst of ventricular
9 tachycardia that went on for 20 seconds, it's listed
10 here. We haven't broken down into severity yet, so
11 you have to keep that in mind when we're looking at
12 this data.

13 Essentially the AV block data, there was
14 no difference between any of the three treatment
15 groups. We did do a chi-square and a Fischer Test on
16 these just to see if there were differences between
17 groups.

18 We found no differences in the occurrence
19 of AV block, ventricular arrhythmias. We had no
20 incidents of ventricular fibrillation in this
21 particular portion of the study.

22 The onset of seizures was within seconds

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1 of ending the injection. Either a few seconds before
2 or a few seconds after. And no deaths in this portion
3 of the study. Based on this data, we see virtually no
4 difference between these three drugs.

5 This is the second portion of the study
6 which was conducted 48 hours after the first portion
7 of the study.

8 This involved injecting two types of
9 convulsive dose, because of the volume, and we wanted
10 to keep the rate relatively constant. These ere
11 injected over approximately 60 seconds.

12 Again, we had some slight differences in
13 the AV block but not significant.

14 Again, same thing with ventricular
15 arrhythmias. Three out of six, five out of six, and
16 one out of six. Statistically, there is no difference
17 there.

18 The incidents of ventricular fibrillation,
19 again, there is a slight distribution between the
20 three groups, but statistically not significant.

21 Onset of seizures generally occurred when
22 about half the dose was administered. Obviously, this

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1 is two times the convulsive dose. We tried to keep
2 the rate relatively constant.

3 So that, seizures were occurring at the
4 time drug was being infused. So, it's a rather severe
5 situation if you look at a clinical scenario.

6 As far as resuscitation. If you look in
7 the last column we had two out of six animals in this
8 particular group die. They both died of ventricular
9 fibrillation. One out of six in this group died and
10 we had no deaths in this group.

11 As far as treatment, we were generally
12 successful in treating a majority of the toxicity,
13 which was primarily CNS, with barbiturate and oxygen
14 ventilation. We've been relatively successful in
15 that.

16 There are two animals, one in this group
17 and one in this group that had ventricular
18 tachycardia, which we were able to successfully treat
19 with Bertyllium and amranone.

20 And we had very little success treating
21 any of the animals that developed VF; we had no
22 success, in fact. And that included chest

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1 compressions, DC cardioversion, and all the drugs that
2 we have available.

3 DR. WATCHA: A question for you. Are you
4 going to continue recruiting more dogs in this study?

5 DR. FELDMAN: The protocol is completed
6 for this study and we have, at this time we have no
7 intention of adding any additional.

8 DR. WATCHA: The reason I asked that is
9 that you have got here a situation where you have got
10 five out of six in one group, whatever that group is,
11 having ventricular arrhythmias, as opposed to one out
12 of six in the others.

13 If that continues on, I'm pretty sure it
14 will reach a point of statistical significance,
15 whatever those two groups are.

16 DR. FELDMAN: I think that that may be
17 true; however, I think that the severity of these,
18 what these numbers represent -- in fact, I can tell
19 you that one of these animals represents a single
20 premature ventricular contraction.

21 DR. WATCHA: That still leaves four
22 others.

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1 DR. FELDMAN: Excuse me? That still
2 leaves four others, that's correct.

3 DR. WATCHA: And I mean if you're going to
4 state on statistics, just -- I mean, if you are
5 looking at percentages, you are referring to a fairly
6 -- even if you take four out of six, that's a 66%
7 situation there, compared to a 33% in the other group.

8 DR. FELDMAN: Correct.

9 DR. WATCHA: You may have something, if
10 it's more animals.

11 DR. FELDMAN: That may be true. I think
12 my recommendation would be to further analyze the
13 severity and the type of these arrhythmias before we
14 decide to do that. As I said, these are grouped, and
15 we haven't looked at severity or duration or anything
16 yet.

17 We occasionally even see PVCs in the pre-
18 drug control on some of these animals, and AV block,
19 also. So it really has to be further analyzed.

20 But statistically, I think you are
21 probably correct.

22 DR. WATCHA: Which brings one other

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1 question, Madame Chairman. Are we going to be voting
2 on acceptance otherwise of this drug, based on what
3 has been presented, or is this just an ongoing, one in
4 a series with regard to this drug?

5 DR. HORLOCKER: Specifically, we are asked
6 to address the two questions that we were sent
7 regarding the labeling of this drug, and we will make
8 our recommendations to the FDA members, based on the
9 data we see today, and whether we require additional
10 studies before the actual labeling can be finalized.

11 So, the answer is --

12 DR. WATCHA: Perhaps this is not the time
13 to discuss it.

14 DR. HORLOCKER: Correct. We'll defer that
15 until later.

16 DR. WATCHA: I'll pick up at that point,
17 then.

18 DR. FELDMAN: Anyway, to conclude the,
19 again, the incidence of deaths and ventricular
20 fibrillation in these, were not statistically
21 significant between the three groups.

22 DR. GENNERY: Can I ask Dr. Mather back to

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1 the podium, because he pointed out in his studies some
2 differences in the types of arrhythmias that developed
3 and how they behaved.

4 DR. MATHER: Dr. Horlocker, Committee,
5 once again, the issue of -- return to the point of
6 convulsant and the arrhythmogenic doses, the
7 fatalities.

8 I was looking here at my data from Study
9 1249107PH in which we have studied the so-called
10 extended series. I note here from my notes here that
11 at doses of 200, 250, 300, and 350, respectively, the
12 main convulsive doses were 111, 123, 136, 137. Quite
13 consistently low levels of the onset of convulsions.

14 And as we know, no animals died of 200 mg.
15 Seven out of ten animals survived 250 mg. Three out
16 of seven animals survived 300 mg, but none out of
17 three survived 350 mg.

18 So, I believe there is quite a significant
19 separation between the CNS for frank convulsions, and
20 the cardiovascular. In fact, fatality is not going to
21 occur.

22 Returning one more point to the issue in

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1 Study 055, where the arrhythmias that were generated
2 in the levobupivacaine group all returned
3 spontaneously to normal rhythm, whereas the animals
4 treated with bupivacaine, as we saw, several of them
5 died with ventricular fibrillation at the same doses
6 that they survived levobupivacaine.

7 So, does that clarify the point you were
8 raising there? I think the literature became a little
9 confused about these deaths. I doubt very much
10 whether a serious analysis of the situation would
11 really support that position.

12 DR. HORLOCKER: In the clinical studies,
13 then with the human volunteers, did you see, did the
14 symptomatology occur at the same dose of
15 levobupivacaine and bupivacaine, but the effects were
16 of lesser magnitude, of shorter duration, or did they
17 occur at statistically different doses?

18 What I am asking, is there a margin of
19 safety, if you do have an intravascular injection,
20 could you give more levobupivacaine before you would
21 see any symptoms, compared to bupivacaine? Do you
22 have any data to evaluate that?

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1 DR. GENNERY: Do you want to --

2 DR. NIMMO: Thank you. My name's Nimmo
3 and I'm from Inveresk Research. I could respond to
4 that with regard to the volunteers.

5 In the first study, one of the volunteers
6 had no CNS side effects, despite receiving 150 mg of
7 levobupivacaine.

8 It was designed, as you remember, to be
9 given until they had CNS side effects, or a maximum
10 dose of 150. Whereas all the volunteers in the
11 bupivacaine group had CNS side effects.

12 In the second study, where it was a
13 parallel group study, all 11 volunteers in the
14 bupivacaine group had CNS side effects, but only 6 of
15 the 11 in the levo group had CNS side effects before
16 the maximum dose was achieved

17 So, it does seem you can give more
18 intravenously before CNS side effects are seen with
19 levobupivacaine.

20 DR. HORLOCKER: And that's a statistically
21 different --

22 DR. NIMMO: Those were small numbers and

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1 that was not tested.

2 DR. HORLOCKER: Are there any other
3 questions from the Committee?

4 DR. DiMARCO: I have a couple of
5 questions, if I might. Dr. Mather, could you explain
6 the dosage on your sheep studies? Were those done,
7 did each animal receive multiple doses, and were they
8 done on separate days, or were they on the same day,
9 with a wash-out period, or were they rapid sequence?
10 I couldn't tell from your presentation.

11 DR. MATHER: Sorry if that was unclear.
12 No animal had more than one dose on a day. There is
13 always at least 24 hours between subsequent doses.

14 The principles of all of those studies I
15 designed are single dose studies. Dr. Santos' study
16 was a cumulating study, but my own studies were each
17 a single dose, no attempt to resuscitate animals. It
18 was to observe the time course.

19 So, all the low dose and the high dose
20 studies were one dose per day, at a maximum per
21 animal.

22 DR. DiMARCO: And one of your endpoints

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1 was number of arrhythmias.

2 DR. NIMMO: Yes.

3 DR. DiMARCO: And I mean, one episode of
4 VF to me is worse than 400 PVCs.

5 DR. NIMMO: I accept that, indeed. We
6 were looking for a comparative scoring system, indeed,
7 and we did characterize the numbers and the data were
8 complex, and I have not presented them in a slide, but
9 certainly, the range of rhythms, or arrhythmias, that
10 were demonstrated by the two sets of animals, they
11 were in each case.

12 There were, you know, ventricular
13 tachycardia bigeminies and trigeminies and that kind
14 of thing demonstrated; however, the multiform
15 ventricular tachycardia was the most significant
16 leading on towards VF, and that was the predominant in
17 the lower doses of the bupivacaine series.

18 And also, in the so-called extended dose,
19 the higher doses, where there was quite a large dose
20 range given, between 250 and 300 mg, that was more
21 likely to occur. Dr

22 DR. HORLOCKER: Dr. Savarese.

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1 DR. SAVARESE: I think in all of the
2 comparative studies that have been reported today, the
3 comparisons are in terms of milligrams of
4 levobupivacaine versus milligrams of racemic
5 bupivacaine.

6 And I guess the data is fairly convincing
7 that there is a difference in the cardiovascular and
8 CNS relative safety when you compare the two drugs,
9 milligram for milligram. And that means the key issue
10 simply is, what is the potency difference between the
11 two, if any?

12 Now, that is my question. In the
13 presentations that were made of the human studies, the
14 clinical studies, the two gentlemen who reported those
15 studies were reporting them as though they considered
16 the local anesthetic potencies of levo and racemic
17 bupivacaine to be identical. So, that is my first
18 question.

19 In humans, are we sure that the local
20 anesthetic potency of each of those two drugs is
21 identical? That 0.5 mg/kg of one -- I'm sorry, 0.5%
22 of one equals 0.5% of the other, in terms of ability

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1 to do a brachial plexus block or an epidural or a
2 whatever. My first question.

3 DR. GENNERY: Can I ask Dr. Kopacz to
4 respond to that, please?

5 DR. KOPACZ: I guess I will give you two
6 answers to that question. One is, just a clinical
7 impression, and that is, since the studies were all
8 blinded, and I did one of the studies, clinically,
9 they are indistinguishable. You didn't know what drug
10 you were going to do.

11 Statistically, and I'm not a statistician
12 but looking through the concerns of the statistician
13 about the studies that were designed for equivalence,
14 and three of the studies that I performed were
15 designed to show equivalence, and there were some
16 methodology errors in -- not errors, but methodology
17 assumptions that were wrong in the first two, but the
18 third one did show equivalence.

19 Actually, all three showed equivalence.
20 In the first two, which were the C Section studies,
21 the assumption that was used to demonstrate
22 equivalence was a ten-minute difference, but the data

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1 that was used to derive that was 18 minutes and onset.

2 So, it was felt that if the onset was less
3 than eight minutes or more than 28 minutes, it would
4 be different.

5 DR. SAVARESE: I, I mean, I'm not
6 quibbling with your data --

7 DR. KOPACZ: Okay.

8 DR. SAVARESE: -- I mean, I think the
9 human data that you presented is quite convincing,
10 also, in terms of equivalent potency, and I'm just
11 asking for some reassurance from yourself and Dr.
12 Crews, that your feeling as clinicians is that you get
13 the same effect from equal quantities, milligrams,
14 total milligrams given to the patients, of the two
15 drugs.

16 Because then that sets up the impression
17 that the safety ratio does seem to be greater for levo
18 than for racemic bupivacaine.

19 DR. KOPACZ: Well, I won't speak for Dr.
20 Crews, but I guess the first statement that I made was
21 my clinical impression, that in doing a double-blind
22 study, you couldn't tell which drug was which.

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1 DR. SAVARESE: Okay. Then, how about Dr.
2 Crews?

3 DR. CREWS: The studies that I did using
4 levobupivacaine were not blinded comparison studies,
5 and I do have experience with the 0.75% for surgical
6 anesthesia and epidural, 0.25% for continuous epidural
7 infusion for post-op, and the use of 0.5% for axillary
8 brachial plexus block.

9 And to me, I saw no evidence that there
10 was any difference in terms of -- again, I hate to get
11 into this semantics issue around potency, but when you
12 are referring to potency, are the two drugs
13 equipotent, I think what we need to define is, that we
14 are talking about the same amount, same concentration
15 of drug producing the same sensory block effect.

16 I think what is important to point out is
17 that there are some very subtle differences between
18 these drugs that you can tease out in terms of things
19 like time to onset, kinetics differences, duration of
20 motor block, and the relative sensory motor block,
21 these types of things that really cloud the potency
22 picture, but in terms of the clinical use of

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1 levobupivacaine versus bupivacaine, my impression is
2 that they would be used at the same doses and
3 concentrations that we are clinically using now.

4 DR. SAVARESE: Okay, let me just follow-
5 up. I mean I am not trying to split hairs here, I
6 agree with both of your presentations, and I'm just
7 looking for more reassurance, that's all. And what we
8 are really interested in here is safety ratios, you
9 know, that's the key issue.

10 So, I think that answers my questions on
11 the human data. I have the same sort of questions
12 about the animal data. All those comparisons were
13 made, sort of milligram for milligram, and didn't
14 address relative local anesthetic potencies in animal
15 species.

16 It would be nice to see that sort of
17 comparison made, together with the relative potency
18 data as well. Just -- it's a very simple question, do
19 we have demonstration in animals that the local
20 anesthetic potency of levo versus racemic bupivacaine
21 is the same?

22 DR. GENNERY: Yes, we do. We can show you

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1 a few slides to --

2 DR. SAVARESE: Don't need to. That's all
3 I need is that kind of reassurance.

4 DR. HORLOCKER: Go ahead.

5 DR. WATCHA: With regard to a particular -
6 - speaking about problems with toxicity, there's a
7 particular patient population where there is a
8 problem, and two years ago when we sat over here, I
9 had requested some information about that.

10 That is, the children below the age of six
11 months, who have a greater tendency to develop
12 problems, particularly with the infusions of
13 bupivacaine. Will you be presenting such data? Do
14 you have any studies on the way to collect such data?

15 DR. GENNERY: Yes, we have two completed
16 pediatric studies, one of which was filed with the
17 NDA, another one of which, safety data was presented.

18 Since the 120-day update period, we have
19 moved a lot further forward with those studies, and we
20 are able to show you, if you would wish to --

21 DR. WATCHA: Now, let me be very specific.
22 We are not asking for a single dose comparison of

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1 local blocks, or a single dose caudal block. I was
2 asking you two years ago for data on continuous
3 infusions, because the patients who would develop
4 toxicity in the pediatric age group, are the younger
5 ones who have got continuous infusions for a period of
6 time.

7 And do you have data on such, or are you
8 planning such studies?

9 DR. GENNERY: Such studies are underway,
10 and we have accumulated a certain amount of data
11 already. If you would like to see where we stand on
12 that, Dr. Joel Guenther, who is one of our principal
13 investigators, could show it to you, or we can show it
14 later in the day.

15 DR. HORLOCKER: Should we show it now?

16 DR. WATCHA: Well, it's up to you, Madame
17 Chair.

18 DR. HORLOCKER: Let's go ahead.

19 DR. GUENTHER: I'm Joel Guenther. I'm a
20 pediatric anesthesiologist at the Children's Hospital
21 Medical Center in Cincinnati, and I have served as a
22 principal investigator and consultant to Chiroscience.

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1 The results I am going to show you right
2 now are part of an ongoing study that is taking place
3 in a multi-center format.

4 Patients are receiving a loading dose of
5 0.175% of bupivacaine, and then are receiving one of
6 four postoperative infusions, 0.125% levobupivacaine,
7 0.0625% levobupivacaine, 0.0625% levobupivacaine with
8 Fentanyl, and Fentanyl alone, and the primary efficacy
9 variable is the proportion of patients requiring
10 rescue in the first ten hours.

11 But, what Meb I think is asking is about
12 safety data in patients under six months, and Kate, if
13 you will show that table.

14 This study is ongoing. It has not been
15 unblinded. We don't know what drugs these patients
16 got. These are the patients under two years who have
17 received infusions of levobupivacaine, presumably
18 three-quarters of them have, and we have this slide
19 here and the other -- Kate, if you will flip -- and
20 what we see is -- go back please -- no reported
21 serious adverse events, and no reported adverse events
22 considered to be possibly related to drug, except for

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1 vomiting.

2 In terms of prolonged infusions in
3 patients under six months, we don't have that. We do
4 have some pharmacokinetics data and some summary data
5 available on a single shot caudal injection of
6 levobupivacaine, including some patients under six
7 months, if you would like to see that.

8 DR. WATCHA: A follow-up question. I
9 noticed that your youngest patient in that list was 11
10 months.

11 DR. GUENTHER: Yes.

12 DR. WATCHA: I see. Thank you.

13 DR. HORLOCKER: Thank you. Any other
14 questions from the Committee?

15 DR. SMILEY: I fear I will belabor the
16 point, but I wanted to approach Dr. Savarese's point
17 in a slightly different way.

18 You have been careful to claim that you
19 are presenting these drugs with equivalent clinical
20 effect and potency, I understand that, but if one is
21 going to make a case or not make a case for the safety
22 issue, the clinical studies you have done have been

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1 done at moderately generous doses, so that were there
2 to be differences in the -- I mean, the epidural
3 doses, the brachial plexus block, were generous.

4 One would expect, you know, clinical
5 efficacy from those doses, even if the drugs were,
6 say, 20, 30% difference in potency. And in fact, in
7 the robivacaine story, a similar kind of story,
8 increased safety, there's been claims of equivalent
9 potency.

10 There is now legitimate controversy in the
11 literature about the relative potency of the drugs,
12 where people claim the difference is as much as 20,
13 30, 40%.

14 So, I guess -- and it maybe the same
15 question and it may be the same answer, and if it is,
16 I don't want to hear it, but is there -- what is the
17 chance that these drugs in fact are different -- have
18 a difference in potency of, say, 25, 30%?

19 I mean, we have to at least keep that in
20 mind as we think about proper labeling and the proper
21 description of the safety factors to the clinicians,
22 so is there any evidence, or are there any plans for

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1 doing studies with this drug, at the limits of its
2 effect?

3 Whatever, whether it's pain management or
4 obstetrics, or areas where you use the drug and get a
5 better sense of when it does work or doesn't work.
6 You are using it in all the studies we have seen,
7 pretty much at doses that would be expected to work,
8 even if differences in potency of 20, 30% were there.

9 DR. GENNERY: Well, I think we could
10 probably tackle that from two or three points of view.
11 And it may be helpful, and if it's not, please say so,
12 to actually show you the preclinical data, which is
13 quite rigorous in the way the experiments have been
14 set up, and then invite our experts back to reinforce,
15 and perhaps address, what is I think the issue that
16 you are raising, whether or not there is a hidden 20%
17 difference there, and which we don't believe there is,
18 and I'm happy to go down whichever path you think is
19 appropriate.

20 DR. SAVARESE: Yes, could I reinforce your
21 question. That was going to be my next question, too,
22 I had one more question, I hate to belabor the issue,

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1 also, but if you are about to present the relative
2 potency data of levo versus dex versus racemic
3 bupivacaine in animals, that is exactly I think what
4 we are looking for.

5 DR. GENNERY: Deborah, could you --

6 DR. HARDING: I'm Deborah Harding,
7 pharmacology, Chiroscience. So, we have evidence that
8 levobupivacaine and racemic bupivacaine are
9 equipotent. And that is at clinically relevant doses
10 in the rat, levobupivacaine, dexbupivacaine, and
11 bupivacaine were found to be equipotent.

12 In a study by Gary Strickartz, looking at
13 sciatic nerve block in the rat, he showed that with .1
14 ml of 0.25% for sciatic nerve block, levobupivacaine
15 and bupivacaine were equipotent on both sensory and
16 motor function.

17 And this dose is equivalent to, that
18 should be approximately 1 mg/kg in the rat. That's
19 about 50% of the clinical dose that was used in the
20 brachial plexus study, and that's Study No. 6154,
21 where about 0.4 mls of 0.5% per kg was used, that's
22 about 2 mg/kg.

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1 Gary Strickartz also looked at cutaneous
2 analgesia in the rat and compared this with the dose
3 used for infiltration for surgery in man. And so
4 here, at clinically relevant doses in the rat,
5 levobupivacaine, dexbupivacaine, and bupivacaine were
6 found to be equipotent.

7 So, for example, with 0.6 mls of 0.075%
8 for cutaneous analgesia in the rat, a similar potency
9 was found, with also a similar duration of action.

10 And this dose that was used in these
11 studies is equivalent to about 2 mg/kg in the rat,
12 which again is similar to that used in the clinical
13 dose for infiltration surgery, and that is for
14 example, in Study 30428, where around 50 mls of 0.25%
15 were given, and that is of the order of 1.8 mg/kg.

16 This is data from the literature, looking
17 at comparing levobupivacaine and dexbupivacaine. The
18 first study is on intradermal anesthesia in the guinea
19 pig, and they compared levobupivacaine with
20 dexbupivacaine.

21 And they showed that levobupivacaine at
22 0.125%, 0.25%, and 0.5% were equipotent, and that

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1 levobupivacaine was 16% more potent than
2 dexbupivacaine at the 0.25%.

3 In spinal anesthesia in rabbits,
4 dexbupivacaine and levobupivacaine were found to have
5 parallel local anesthetic dose response curves.
6 Levobupivacaine was found to be 40% more potent than
7 dexbupivacaine.

8 In corneal anesthesia in the rabbit,
9 levobupivacaine and dexbupivacaine had similar
10 activity.

11 A study done by Aberg in 1972 looked again
12 at sciatic nerve block in frog and rat. And on
13 potency found no difference between levobupivacaine
14 and bupivacaine in vitro frog sciatic nerve, and in
15 vivo in rat sciatic nerve.

16 Also looking at infiltration anesthesia in
17 the guinea pig, levobupivacaine had a longer duration
18 of anesthesia than bupivacaine, and it was significant
19 at 0.25%.

20 Another study by Dhyre recently published,
21 or fairly recently published, on infraorbital nerve
22 block in the rat. He found here that the duration of

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1 infraorbital nerve block was slightly lower at 0.125%
2 for levo than bup, but at 0.25% and 0.5% -- that's a
3 typing error there -- they were equipotent.

4 DR. HORLOCKER: Any other questions?
5 We'll take more question then defer the rest for our
6 discussion later in the afternoon. Dr. Parris?

7 DR. PARRIS: Winston Parris, Tampa,
8 Florida. In pain management situations, one usually
9 pre-treats the patients with benzodiazepines, either
10 diazepam or midazolam, not only for sedation, but also
11 for elevating their seizure threshold in the event of
12 an inadvertent intravascular injection.

13 Did any of your, in your clinical studies,
14 did you pretreat those patients with diazepam or
15 midazolam, prior to determining your cardiotoxicity,
16 and also your neurotoxicity studies?

17 DR. GENNERY: Well, I think in terms of
18 the volunteer studies, they had no medication other
19 than test medication at all.

20 DR. PARRIS: And so the lidocaine, the
21 lidocaine test.

22 DR. GENNERY: Yes, well, the lidocaine

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1 test was done one week prior to them going into the
2 formal part of the study, but one of the requirements
3 to the protocol is that they should have no other
4 medication whilst participating in those studies.

5 So, the only agents they got were either
6 bupivacaine or levobupivacaine, nothing else.

7 DR. PARRIS: What about the animal
8 studies, did you --

9 DR. GENNERY: Sorry, which ones?

10 DR. PARRIS: In the animal studies.

11 DR. GENNERY: Well, Robert, can you --

12 DR. GRISTWOOD: Can I ask you to please
13 repeat the question.

14 DR. GENNERY: What other medications were
15 given as part of the animal study protocols, the whole
16 animal models, I guess you are referring to --

17 DR. PARRIS: Yes.

18 DR. GENNERY: -- both the pig and the
19 sheep. The anesthesia in the pig model?

20 DR. GRISTWOOD: That was pentobarbital.

21 DR. GENNERY: Pentobarbital was the
22 anesthesia in the pig model, and the sheep were --

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1 DR. GRISTWOOD: The sheep were not --

2 DR. GENNERY: -- conscious during the
3 experimental phase of the study.

4 DR. HORLOCKER: Thank you. We'll just
5 take a quick break and reconvene at -- I'm sorry, go
6 ahead.

7 DR. ROBERTS: I'm sorry, one quick
8 question. I had a question for Dr. Crews. You
9 mentioned in your study that you had found some
10 evidence of an improved cardiovascular and CNS
11 profile.

12 Can you please give us the study numbers
13 and whether those studies were ongoing at the time of
14 NDA submission?

15 DR. CREWS: I would assume you are
16 referring to my conclusion that, based on the data we
17 have from the clinical safety, clinical trial
18 database, that there seems to be evidence to support
19 the fact that levobupivacaine may have less
20 cardiotoxicity or CNS toxicity.

21 The studies that I am referring to with
22 respect to CNS toxicity was the human volunteer EEG

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1 study, MAO 400. The cardiovascular safety data would
2 include the meta analysis from the four clinical
3 trials that were listed.

4 They were CS 001, CS 005 -- I had it on my
5 slide, but I don't recall the --

6 Yes. The meta analysis included the two
7 pharmacology studies which were 004801, 012105, and
8 then the clinical studies that were included in this
9 with signal averaged EEG -- EKG data were CS 001, CS
10 005, 030632, and 030721.

11 The evidence for enhanced cardiovascular
12 safety from that meta analysis being less effect on
13 prolongation of the PR interval, and the additional
14 data supportive of differences in CNS and
15 cardiovascular effects are based on the response to
16 the suspected intravascular injection data that I
17 presented.

18 DR. ROBERTS: Thank you.

19 DR. HORLOCKER: We will take a ten-minute
20 break and reconvene at 11:35.

21 (Whereupon, at 11:25 a.m., a brief recess
22 was taken until 11:37 a.m.)

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1 **FDA Presentation**

2 **Summary of the Issues**

3 DR. RAPPAPORT: Good morning, Dr.
4 Horlocker, members of the Committee. My name is Bob
5 Rappaport. I am the Deputy Division Director of the
6 Division of Anesthetics, Critical Care, and Addiction
7 Drug Products, and I am also the Team Leader for the
8 Anesthetics Drug Group.

9 I want to thank the Sponsor for allowing
10 us to give you a relatively short presentation today.
11 And I have a couple of things I need to point out
12 before we start.

13 The first is that, for the record, Dr.
14 John DiMarco from the Cardiovascular Advisory
15 Committee has been consulting with us during the
16 review process, and is serving as a nonvoting member
17 of the Committee today.

18 The other issue that I wanted to point out
19 was a few places in the Sponsor's presentation where
20 we hadn't had a chance to review the data, and the
21 first of that is, obviously the dog resuscitation
22 study.

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1 The second is the pediatric study data
2 presented by Dr. Guenther. And I want to also point
3 out that the, I think it was six studies that Dr.
4 Crews included in the meta analysis, we only received
5 four studies in the integrated analysis that we
6 reviewed. There's a little bit of difference there.
7 I don't know if that's --

8 We are asking your help today in answering
9 two questions. The first question is, Has the Sponsor
10 done an adequate and appropriate job of evaluating the
11 cardiotoxicity of their product?

12 The second question is, Would it be
13 appropriate for the Agency to approve labeling for
14 that product, which does not begin with a black boxed
15 warning regarding the potential cardiotoxicity with
16 the 0.75% concentration, particularly in the
17 obstetrical patient?

18 The only purpose we have in asking these
19 questions is to allow us to write labeling that
20 provides for the safest and the most effective use
21 possible.

22 We are in concurrence with the Sponsor

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1 regarding the effectiveness of levobupivacaine, while
2 the actual potency, in comparison to bupivacaine and
3 other related local anesthetic agents, has not been
4 fully elucidated in our opinion, it does appear to
5 provide effective anesthesia in the settings which
6 have been studied thus far.

7 The Sponsor claims equivalent potency to
8 bupivacaine, however, their application contains a few
9 instances in which levobupivacaine appears to be less
10 potent than bupivacaine, and no absolute documentation
11 of equivalence has been recorded in any setting.

12 You have heard an extensive and detailed
13 presentation from the Sponsor. What we are asking you
14 to consider now are a number of factors which have
15 combined to prevent us from coming to a final
16 conclusion on our own regarding the issue at hand.

17 The first portion of our presentation
18 covers what we don't know at this time from the
19 preclinical evaluations that were undertaken by the
20 Sponsor at this Committee's recommendation.

21 Dr. Goheer, the Reviewing Pharmacologist
22 for this application, will present that information.

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1 That will be followed by comments from Dr. Roberts,
2 the Primary Medical Reviewer for the application, and
3 she will give you the Division's perspective on the
4 safety data, and analyses submitted to the
5 application, highlighting the areas where our
6 interpretation differs from that of the Sponsor.

7 And the final portion of our presentation
8 will come from Dr. Permutt, the Supervisory
9 Biostatistician on this product. Dr. Permutt will
10 address the important matter of the relative potency
11 and toxicity of levo and racemic bupivacaine, which
12 you all obviously are aware of already.

13 In answer to our first question, Has the
14 Sponsor adequately evaluated levobupivacaine's
15 potential for cardiotoxicity at the labeled dose, and
16 if not, what further studies are needed?

17 You may conclude that enough data is
18 available already, or that more is required. I would
19 ask that if you choose the latter, you help us
20 determine what more is required, and at what point we
21 can allow the Sponsor to claim an improved cardiotoxic
22 profile for their product, assuming of course that

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1 their hypothesis is correct.

2 For our second question, Should the boxed
3 warning that currently exists in the bupivacaine
4 label, be applied to this product?

5 There are three possible answers. The
6 first, have the black box for bupivacaine, for
7 levobupivacaine, read just as it does for bupivacaine.

8 The second possibility is, make specific
9 changes in the black box for levobupivacaine, and
10 perhaps bupivacaine as well. An example of that would
11 be, removing the reference to any specific
12 concentration.

13 Finally, you can choose to recommend not
14 using a black box at all for this product.

15 In considering your answers to these
16 questions, I would ask that you be aware of two
17 matters with which the Division must concern itself in
18 our review of the labeling for this product.

19 The first is, we must provide a level
20 playing field for all products with relatively
21 equivalent safety and efficacy risk-benefit ratios,
22 especially products in the same pharmacologic class,

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1 and with similar mechanisms of action.

2 The second matter is, how our actions
3 produce changes in the medical community, at times
4 unintentionally. By not including a strongly worded
5 black box in the labeling for levobupivacaine, and
6 even possibly removing or changing the black boxed
7 warning in the bupivacaine labeling, are we sending
8 practitioners a message which may result in an
9 increased risk to their patients?

10 We appreciate your assistance in helping
11 us reach an appropriate conclusion regarding the
12 labeling of this new product. And we will begin with
13 Dr. Goheer.

14 **Preclinical Cardiac and Neurotoxicity**
15 **Issues**

16 DR. GOHEER: Good morning, Dr. Horlocker,
17 ladies and gentlemen. My name is Anwar Goheer. I am
18 a pharmacologist at FDA.

19 To save time, I will not address the data
20 already presented by Dr. Gristwood and Professor
21 Mather. They have presented the data nicely.

22 As you know, the Sponsor claims that the

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1 levobupivacaine is as effective as bupivacaine. Data
2 presented by the Sponsor also indicate that the
3 levobupivacaine had less cardiovascular toxicity than
4 bupivacaine.

5 Bupivacaine is a racemic compound and it
6 has been used for many years as a local anesthetic.
7 At high concentration, it causes CNS and
8 cardiovascular toxicity, hypotension, cardiovascular
9 collapse, and ventricular arrhythmia have been
10 reported in the literature.

11 Nearly two years ago, we had a meeting of
12 this Advisory Committee on this topic. It was agreed
13 that the data from the following studies are needed to
14 compare the cardiovascular toxicity of levobupivacaine
15 and bupivacaine.

16 These studies will help us to understand
17 the direct effect on the myocardium and the CNS, and
18 the role of the CNS on cardiotoxicities.

19 These studies will also show the relative
20 ease of resuscitation in the animals. These studies
21 are comparisons of the direct effect of
22 levobupivacaine and the racemate on the CNS and the

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1 heart, and conscious sheep, following closed, intra-
2 arterial injection.

3 Specifically, we can divide that into two
4 categories. Number one is the heart direct coronary
5 artery infusions. In this study, the CNS performance
6 was maintained.

7 Professor Mather has completed coronary
8 artery infusion studies with the levobupivacaine,
9 bupivacaine, and ropivacaine in sheep. The final
10 reports have not been submitted to the FDA.

11 The second category was CNS direct carotid
12 artery infusions with cardiac performance maintained.
13 The intra-carotid and the resuscitation studies in
14 sheep have not been started.

15 Number two was to simulate clinical
16 resuscitation following bolus administration of a
17 little dose.

18 According to the Sponsor, the experimental
19 phase of dog resuscitation study has been completed.
20 These are the preliminary data presented by Dr.
21 Feldman this morning.

22 The final report of this important study

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1 has not been submitted to the FDA. The data from
2 these important studies are needed to conclude that
3 levobupivacaine is less cardiotoxic than bupivacaine.

4 Conclusions. Animal studies show
5 preliminary evidence of differential cardiotoxicity.
6 That is levobupivacaine may have better cardiovascular
7 safety profile than bupivacaine.

8 However, the main question that remains to
9 be answered.

10 Question No. 1, what are the direct
11 effects on myocardium and CNS and the role of CNS on
12 cardiotoxicity?

13 Question No. 2, what is the relative
14 difficulty of resuscitation in the animal?

15 We are waiting for the data from these
16 important studies that I just mentioned. We would
17 like to seek the expert opinion and comments from this
18 Advisory Committee on this issue.

19 Thank you. And now I will invite Dr.
20 Monica Roberts to present her clinical review.

21 **Clinical Cardiovascular and Neurotoxicity**
22 **Issues**

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1 DR. ROBERTS: Good afternoon, Dr.
2 Horlocker and members of the Committee. My name is
3 Dr. Monica Roberts and I am the Primary Medical
4 Reviewer for this NDA.

5 I will be presenting to you the
6 cardiovascular safety as I saw it, as submitted in the
7 NDA. I will try not to repeat any of the specific
8 data that was already presented by the Sponsor.

9 The clinical development program of
10 levobupivacaine was specifically designed to evaluate
11 the product's effects on cardiovascular function.

12 The Sponsor has designated five clinical
13 trials and one integrated analysis of four of these
14 trials to determine and compare the effects of
15 levobupivacaine and bupivacaine, specifically on QT
16 dispersion, and QRS intervals.

17 The integrated analysis included Study
18 004801, as you can see. In the remaining studies, I
19 won't repeat them to you.

20 The analysis of the four separate clinical
21 trials were designed with the following objective. To
22 determine the effects on QT dispersion or QRS

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1 interval, following exposure to study drug, the
2 hypothesis being that levobupivacaine had little
3 effect on cardiac electrical parameters.

4 Study 004801 was a double-blind,
5 randomized, crossover study, and subjects dosed with
6 intravenous bupivacaine, or levobupivacaine, to CNS
7 symptomatology.

8 The primary endpoint was the difference in
9 QT dispersion from pre-dose, to the maximum observed
10 post-dose value.

11 The results show that the estimate of the
12 treatment difference was -5.4 ms, which was not
13 statistically significant.

14 Neither were the secondary endpoints, PR
15 intervals, QRS intervals, and QT intervals, found to
16 be statistically significant.

17 Study CS 005 was also conducted in a
18 double-blind, randomized fashion, and it compared
19 0.75% levobupivacaine to the same dose of bupivacaine.

20 The primary endpoint was the difference in
21 QT dispersion from pre-dose to the maximum observed
22 post-dose value; however, the QRS data were those upon

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1 which statistical analyses were performed.

2 The results showed that the estimate of
3 the treatment difference was -0.4 ms, which again was
4 not statistically significant.

5 Study 030721 compared 0.25%
6 levobupivacaine with 0.25% bupivacaine. The primary
7 endpoint was the difference in QT dispersion from pre-
8 dose to the maximum observed post-dose value.
9 Statistical analyses were performed on the QRS data as
10 well.

11 The results showed that the estimate of
12 the treatment difference was -1, which was not
13 statistically significant.

14 The last Study included in the meta
15 analysis, Study 030632, compared 0.5% levobupivacaine
16 and bupivacaine. The primary endpoint again was the
17 difference in QT dispersion from pre-dose to the
18 maximum observed post-dose value.

19 The results showed that the estimate of
20 the treatment difference was -1.09, which was not
21 statistically significant.

22 The second endpoints of PR intervals, QRS

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1 intervals, and QT intervals were also not
2 statistically significant.

3 Additionally, Study 012105 was submitted
4 as evidence of cardiovascular safety, although not
5 included in the meta analysis, was a two-phase
6 analysis of the cardiovascular effects of
7 levobupivacaine when administered intravenously in an
8 open label fashion, followed by a double-blind,
9 randomized, evaluation of the effects of
10 levobupivacaine and racemic bupivacaine on myocardial
11 depolarization, and re-polarization, as measured by
12 QRS duration of a signal averaged EKG, and QT
13 dispersion in healthy males.

14 In this Study as in the previous EKG
15 study, subjects were dosed to CNS symptomatology. The
16 objective of this Study was to compare the QT
17 dispersion from a blinded review, as well as PR, QT,
18 QTc, and signal averaged QRS durations, by dose.

19 The primary endpoints were the maximum
20 positive change from pre-dose, using the end of
21 infusion, 5 minute, 10 minute, 15 minute, and 30
22 minute time points for the QT dispersion and the

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1 signal averaged QRS values for each treatment.

2 Secondary endpoints for the same time
3 points were PR, QT, and QTc durations for each
4 treatment.

5 The Sponsor concedes that there are no
6 statistically significant changes from baseline in the
7 primary endpoints, QT dispersion and QRS duration, or
8 for the secondary endpoints, changes from baseline in
9 the PR and QT intervals, between the two treatments,
10 however while there did appear to be a statistically
11 significant difference between the two treatments with
12 regard to the change in baseline in the QTc, this
13 endpoint was chosen prospectively to be secondary in
14 nature, and was just one isolated finding among many
15 other endpoints which were shown not to be
16 statistically significant.

17 Dr. John P. DiMarco is the Director of
18 Clinical Electrophysiology Lab and Associate Division
19 Head, Cardiovascular Division, at the University of
20 Virginia.

21 He consulted with the FDA on the
22 evaluation of the cardiovascular safety of

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1 levobupivacaine. I will defer to him to present his
2 conclusions as an independent reviewer of these
3 studies.

4 My search strategy for identifying the
5 significant cardiovascular adverse events was to
6 perform a head-to-head comparison of all reported
7 cardiovascular adverse events in the levobupivacaine
8 clinical development program.

9 The following data was obtained from the
10 safety database, however the data from the safety
11 update was not included in time for this meeting.

12 As you can see from this slide, there is
13 very little difference in the percentage of
14 cardiovascular events reported between the two groups.

15 Secondly, I separated the clinical trials
16 according to category, and found the following similar
17 results. In the obstetric population, there again,
18 was -- we were not able to appreciate any difference
19 in terms of the cardiovascular events that were
20 reported.

21 Of interest, is the incidence of
22 bradycardia, percentages being eight to zero in favor

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1 of bupivacaine, however the number of patients in each
2 group must be taken into consideration.

3 In the pain management population, again
4 the two drugs are behaving similarly, however with the
5 incidence of tachycardia, bupivacaine demonstrated a
6 twofold increase in cases reported. Based upon this
7 one isolated finding, however, one cannot conclude
8 that there is clear evidence that bupivacaine in this
9 case is less safe, either.

10 The analysis of the cardiovascular adverse
11 events reported in the Peripheral Block Study
12 demonstrated the same overall trend.

13 Finally, in the Pediatric Study, when
14 patients received either levobupivacaine, or no local
15 anesthetic at all, the cardiovascular adverse events
16 occurred only in the levobupivacaine group.

17 Next, I chose one cardiovascular adverse
18 event, namely, bradycardia, and gathered as much
19 details of the surrounding episode as possible.

20 I chose bradycardia because it occurred
21 with a fair amount of frequency; i.e., less than 5%,
22 and it was associated with asystole on at least two

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1 separate occasions.

2 The first episode occurred in a 66 year
3 old male with a history of essential hypertension for
4 which he took atenolol and naproxen for
5 osteoarthritis.

6 He was scheduled to undergo a knee
7 replacement. He received a T12 to L1 epidural with 10
8 mls of 0.125% levobupivacaine. It was given in
9 divided doses.

10 As you can see, his pre-op EKG was
11 significant for sinus rhythm, however his heart rate
12 was 55, blood pressure was normal, and saturations as
13 well.

14 Following drug administration, ten minutes
15 following exposure, as you can see, his heart rate had
16 dropped to 40 bpm. He subsequently was unarousable
17 and had a flat line EKG. He was resuscitateable,
18 however.

19 The sensory block at that time was found
20 to be T6 to T7. It was said to have increased to T3
21 to T2, subsequently. One can conclude that this may
22 represent the possibility of a high spinal, and

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1 equally, one can conclude that this represents study
2 drug effect.

3 The next case involved a 46 year old
4 female with a history of GI reflux, anemia, and renal
5 carcinoma, and also a pre-op EKG suggestive of mild
6 bradycardia.

7 She was scheduled to undergo a radical
8 nephrectomy and received a total of 12 mls of 0.75%
9 levobupivacaine.

10 Inter-op course was significant for the
11 occurrence of a pneumothorax. As they dissected the
12 abdomen, they entered the diaphragm.

13 In the recovery room, however, as you can
14 see, her vital signs were relatively similar to pre-
15 op, and she complained of pain and received a bolus
16 administration of 0.75% levo, followed by an infusion,
17 and one hour following administration, she was
18 complaining of nausea and as she vomited, she then
19 went into asystole, however she also was
20 resuscitateable.

21 Conclusions. Two conclusions are
22 possible. One, that this represents a vasovagal

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1 response, or two, that this represents drug exposure,
2 the effects of drug exposure.

3 The next case involves the only death that
4 occurred in this study, a 70 year old male with a
5 history of GI disorder, scheduled for left hip
6 surgery.

7 He underwent an epidural of 0.75%
8 levobupivacaine bolus, followed by the study drug
9 infusion, which in this case included the additional
10 administration of clonidine.

11 His pre-op EKG was similar to that post-
12 op, which demonstrated left ventricular hemi-block.
13 Pre-op vital sounds were normal, however, one hour
14 following administration of study drug, he
15 demonstrated blood pressures of 50s to 60s, which
16 remained so for the ensuing 27 hours of his hospital
17 stay.

18 EKG, as I stated previously, showed a left
19 axis deviation on discharge. The patient expired 11
20 days following treatment.

21 The one case that I would like to present
22 to you of pediatric bradycardia, occurred in a five

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1 year old male who had a history of enteritis, and
2 surgical correction of an anal rectal abscess. He
3 also had, in the past, myringotomy with tubes.

4 He was scheduled to undergo a left
5 inguinal hernia repair, and received 0.5%
6 levobupivacaine as an infiltration anesthetic. As you
7 can see, his pre-op vital signs were normal for age.

8 Approximately one hour and 30 minutes
9 following study drug administration, he was
10 bradycardic and complaining of nausea and vomiting.
11 This also resolved.

12 In summary, I would like to say that my
13 conclusions are that there are unquestionably some
14 amount of cardiotoxic effects associated with this
15 drug, and I have not been able to find data in the NDA
16 which would allow me to draw any final conclusions
17 that there is a statistically significant difference
18 between the two drugs with respect to the
19 cardiovascular safety.

20 **Potency/Toxicity, and Related Efficacy and**
21 **Safety Statistical Interpretations**

22 DR. PERMUTT: I'm Tom Permutt. I'm Team

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1 Leader for Anesthetics in the Office of Biostatistics
2 at FDA.

3 You have heard from my three colleagues
4 about the three different kinds of data that we have
5 to address the relative potency and toxicity of levo
6 and racemic bupivacaine, and I want to talk about the
7 rather difficult problem, I think, of putting these
8 three kinds of data together and yes, we do think that
9 potency is important.

10 Dr. Rappaport spoke briefly about the
11 clinical efficacy data. Levobupivacaine was compared
12 to bupivacaine, usually at the same doses, in several
13 anesthetic techniques. Both were effective. In fact,
14 both were approximately perfectly effective. The vast
15 majority of the patients had their surgery with
16 adequate anesthesia.

17 In very few studies, higher concentration
18 of levobupivacaine as compared to bupivacaine, and
19 again, not much difference in the response was seen.
20 And again, this is because both were about completely
21 effective.

22 We're in a flat part of the dose response

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1 curve, so these studies are not sensitive assays of
2 potency, they, as the Sponsor told you, they weren't
3 meant to be. They are studies of efficacy and they
4 show that levobupivacaine, like bupivacaine, was
5 effective.

6 Dr. Roberts talked about the
7 electrocardiographic data from several human studies,
8 both observations of the clinical trials in patients
9 and the special studies in volunteers.

10 Our interpretation of these, as Dr.
11 Roberts says, is a little different from that of the
12 Sponsor. Dr. Nimmo and Dr. Crews mentioned how very
13 few statistically significant differences, but these
14 were extracted from a rather large number of possible
15 comparisons, and on the whole, my evaluation is that
16 those don't represent a statistically significant
17 difference in effect.

18 As Dr. Woosley commented this morning, you
19 wouldn't expect to see effects, because humans were
20 very appropriately not dosed to serious toxicity. So,
21 again, you're in the flat part of the dose response
22 curve. This time, the lower end.

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1 We've got the animal toxicity data
2 discussed by Dr. Goheer. And here, we do see
3 differences between the two drugs. Milligram for
4 milligram, as Dr. Savarese says, you see more toxicity
5 with bupivacaine than with levobupivacaine, looking up
6 and down.

7 You get a bewildering variety of
8 percentage differences, or ratios, depending on what
9 exactly it is you are measuring, as a toxicity, and
10 quantitatively, the interesting comparison I think, as
11 Dr. Savarese intimated earlier, is going across.

12 You see roughly equal toxicities at doses
13 of levobupivacaine and of bupivacaine, in roughly a
14 ratio of 1.3:1. More than 25%, not dramatically more
15 than 25%, but more than 25%, less importantly than the
16 ratio of 0.75% to 0.5%.

17 All right, so again, the question is how
18 to put these three kinds of data together. And while
19 studiously avoiding talking about potency, I think the
20 impression that the Sponsor would like to leave us
21 with, and which in fact is what I hope is true, is
22 this. That the efficacy of bupivacaine and

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1 levobupivacaine, the dose response with respect to
2 efficacy are about the same.

3 And that there are differences in
4 toxicity, that bupivacaine is more toxic -- and again,
5 I've schematically drawn these rather far apart, but
6 I remind you that the ratio is only something like 1.3
7 -- so that there is a better therapeutic index, if you
8 will, better separation of effective doses of
9 levobupivacaine, from here to here, and of
10 bupivacaine, from here to here.

11 And I agree that the data are completely
12 consistent with that hypothesis; that we haven't seen
13 anything to controvert that hypothesis. The clinical
14 efficacy data up here. The human toxicity data down
15 here. And the animal toxicity data all in here, which
16 is you know, were you actually see the separation.

17 I also don't see anything in the data that
18 is not consistent with this alternative hypothesis,
19 which is that the potency of levobupivacaine and
20 bupivacaine, the potencies are different by about the
21 same ratio as the toxicities are different, so that
22 the therapeutic index of the two drugs is about the

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1 same.

2 Again, here we have the human clinical
3 data up here in a flat part of the efficacy curve of
4 human toxicity data. And the separation here. But
5 you don't see any separation here, because you don't
6 have any data with which to see it.

7 If this is true, then to the extent that
8 drugs are dosed to effect in clinical practice,
9 levobupivacaine is not a safer drug. I think we can
10 hope that it is, but I don't think that there is
11 anything in the data that allows us to say at this
12 point that we know that it is.

13 I was interested to hear at the end of the
14 Sponsor's presentation, in response to comments, some
15 comments on the animal potency studies. And I don't
16 find them terribly reassuring, either.

17 I think that they suffer largely from some
18 of the same problems as the human studies. You see no
19 difference in effect, where you wouldn't expect to see
20 any difference in effect, because you have maximal
21 effects. And you don't get, you have really rather
22 crude estimates of potency, which I think are not

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1 sufficient to rule out the possibility of what we are
2 talking about, which is a fairly subtle difference in
3 the potency, on the order of -- you know, again, 20,
4 30, maybe 40%, which is what we think the difference
5 in toxicities are.

6 So, again, I hope it's safer, but I don't
7 see any reason at this point to know that it's safer.

8 **Questions From the Committee**

9 DR. HORLOCKER: I would like to thank the
10 FDA for their concise and timely presentation. We'll
11 take questions now. Dr. Savarese.

12 DR. SAVARESE: I think another key issue
13 here that we should ask the Sponsors to give us more
14 reassurance about is the relative potencies and
15 toxicities of levo versus dexbupivacaine.

16 We didn't really get that kind of
17 information from the presentation this morning.

18 DR. GENNERY: Well, we have clearly not
19 studied dexbupivacaine in humans.

20 DR. SAVARESE: And I'm satisfied with
21 animal, yes, I understand. I understand. Perfectly
22 satisfied with animal data.

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1 DR. GENNERY: I think I'll ask Dr.
2 Gristwood if we could put back his summary slide,
3 because there the table did distinguish between those
4 studies looking at racemic, and those studies looking
5 at dex.

6 And then, if Dr. Harding can just again
7 bring those slides back where there is some summary
8 information of where dex has been studied. We'll try
9 and answer that question for you.

10 DR. GRISTWOOD: Okay, this shows the
11 summary slide for the relative cardiotoxicities from
12 the range of studies, the comparative studies that
13 were carried out.

14 I think you can see here that we do have
15 data both for dexbupivacaine compared to
16 levobupivacaine, where we're seeing -- you can start
17 off looking at the in vitro data where we have got
18 sodium channel data, these large differences here
19 between the two isomers.

20 The important comparison here between the
21 racemate and levobupivacaine, and again, we're still
22 seeing a big difference here.

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1 If we look at the, again, coming down
2 through the slides, having data both for
3 levobupivacaine and the racemate, in both instances
4 we're seeing differences between the dexbupivacaine
5 and racemic bupivacaine.

6 In fact, the only study that in vivo that
7 was looking at dexbupivacaine was the rat study, where
8 the differences were huge, there were huge
9 differences.

10 The sheep study, we have data for racemate
11 versus levobupivacaine. The pig study, we compared
12 racemate with levobupivacaine.

13 DR. SAVARESE: Okay, thank you. I
14 apologize. I just didn't remember this column in this
15 particular slide.

16 DR. GRISTWOOD: I think the dexbupivacaine
17 data really helps to reinforce the racemate versus
18 levobupivacaine.

19 DR. SAVARESE: That's what I'm looking
20 for; yes, that's what I'm looking for. And also, your
21 potency estimate for the three compounds, the dex, the
22 levo, and the racemate is identical in terms of local

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1 anesthetic potency. Is that not correct?

2 They do not differ significantly, the
3 three different optical isomers, or mixtures of.

4 DR. GENNERY: This is the study we asked
5 Dr. Strickartz to carry out on our behalf at Boston.
6 And we have, for the purposes of this presentation,
7 really only qualitatively talked about levo and dex,
8 because we felt that probably the most focused
9 discussion from a clinical point of view would be the
10 relative comparison between levo and bupivacaine, and
11 especially if we could relate what Dr. Strickartz did
12 to a clinical type of dosage.

13 But the basic outcome from the study is
14 that the two enantiomers and the racemate behave in a
15 pretty equipotent sort of a fashion, both in the
16 sciatic nerve model, and in his infiltration model.

17 DR. SAVARESE: Right. This is important,
18 because in your basic contention with all of this data
19 is that you have kind of removed the bad medicine, the
20 dexbupivacaine, and left only the good stuff in there.

21 DR. GENNERY: Sure.

22 DR. SAVARESE: One more question about

1 human, you have not given dexbupivacaine to anybody,
2 correct?

3 DR. GENNERY: Absolutely.

4 DR. SAVARESE: Does anybody here have any
5 opinion on -- I mean, to me, it would be a very simple
6 potency comparison to do a very simple peripheral
7 nerve block procedure, you know, like an ulnar nerve
8 block or something, comparison, just to verify to us
9 clinicians that in humans, really, dexbupivacaine and
10 levo have the same potency, and that reinforces
11 further your safety contentions.

12 Does anybody? Yes, Rich?

13 DR. SMILEY: It would be a more -- I mean,
14 assuming you wanted to find the difference, it would
15 obviously be the best way to find the differences that
16 exist, to compare the L to the D, rather than the L to
17 the racemate, because obviously you're averaging two.

18 It's -- again, it's stating the obvious,
19 but I'll reinforce what Dr. Savarese is saying, that
20 if we wanted to really pin down that these are
21 equipotent drugs, if that matters, and it may, in some
22 kinds of studies.

1 There are other things using low doses
2 where you could be overly-worried about the isomer's
3 activity, would really pin that down. Those were very
4 close. It would be hard to make a case if the
5 racemate would be the different --

6 DR. SAVARESE: Yes, I mean, I think that's
7 what we're asking for, is there that kind of a
8 comparison in humans available?

9 DR. GENNERY: The study that Aps and
10 Reynolds carried out in the 1970s was in fact one of
11 the studies which gave us the encouragement to move
12 forward, of showing equipotency.

13 In fact, they felt that they had shown
14 that levobupivacaine was somewhat more potent than the
15 racemate. I can't remember whether dex was included
16 in that paper. Apparently, it was. Perhaps we could
17 dig that out and reread that.

18 DR. HORLOCKER: Yes?

19 DR. JEAN: Lucy Jean, pharmacologist from
20 FDA. In order to understand intrinsic potency, the
21 study as proposed by Dr. Savarese is useful.

22 I would like to point out, the Sponsor

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1 stated equipotency at 0.25%, however at the lower
2 concentration, 0.125, there are differences in the
3 potency. Perhaps the 0.25, we already reached 100%
4 analgesic effect. In order to see a difference, why
5 don't you study at a lower concentration, to establish
6 the intrinsic potency?

7 Thank you.

8 DR. HORLOCKER: Can we have the lights up,
9 please? I have a question for Drs. Roberts and
10 Permutt. Certainly, the laboratory studies show a
11 trend towards decreased cardiotoxicity and as Dr.
12 Smiley mentioned during the break, if he was a
13 pregnant sheep, he would like to receive
14 levobupivacaine rather than bupivacaine.

15 DR. SMILEY: Whether I was pregnant or
16 not, put it that way.

17 DR. HORLOCKER: Yet, we don't have
18 definitive human studies demonstrating this. Is this
19 a lack of power of the studies, that we just don't
20 have enough? Are there trends that may become
21 significant, or do we just not have clinically
22 significant differences between these two drugs, the

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1 way that they have been evaluated at this point in
2 time?

3 DR. PERMUTT: Yes, I think it's that we
4 don't have the right kind of studies. To really see
5 the difference in potency, you would have to give less
6 than what Dr. Smiley called, generous doses, and see
7 what --

8 What we would be looking for is equivalent
9 effects at less than 100%. It doesn't help us much
10 with respect to potency to say that both the drugs
11 were completely effective.

12 If they were both partially effective to
13 the same degree at the same dose, that would help, but
14 we don't really have that kind of study.

15 So, not so much the numbers that are
16 lacking as the studies of different dose, dose ranging
17 design.

18 DR. HORLOCKER: Could we do those studies
19 safely in humans, or would it require such doses that
20 we would be ethically not allowed to do that?

21 DR. SMILEY: Excuse me. Were you talking
22 about toxicity or potency --

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1 DR. HORLOCKER: Yes, the cardiotoxicity --

2 DR. SMILEY: Because he answered to
3 potency, and your real question was about toxicity --

4 DR. HORLOCKER: Right.

5 DR. SMILEY: -- and I think the answer may
6 be that there simply may not be endpoints in humans
7 that -- I mean, the endpoints that you hoped for in
8 the meeting a couple of years ago just don't seem to
9 be real endpoints. Either they are different or they
10 aren't the right endpoints.

11 DR. PERMUTT: I'm sorry, Dr. Smiley is
12 quite correct. I misinterpreted your question, I was
13 thinking about the question of relative potency. I
14 agree with Dr. Woosley that it's probably impossible
15 to study toxicity in humans meaningfully.

16 DR. HORLOCKER: Dr. Reves?

17 DR. REVES: I would agree on ethical
18 grounds, impossible to study that. We could design
19 very simply a relative potency study, I mean, Richard
20 and I already designed one, but I mean, I don't think
21 that would be difficult.

22 You'd start with low doses and you would

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1 have a peripheral nerve, and you would see whether
2 pain is equivalently blocked or not, and I think you'd
3 step up and you'd see -- walk up the whole dose
4 response curve, and you'd compare them.

5 So, I think that's possible. That's all
6 I have to say.

7 DR. HORLOCKER: Yes.

8 DR. CARLISLE: The real question, though,
9 is at a clinically effective equipotent dose, are the
10 toxicities going to be accelerated, and that's the
11 issue in terms of what we were supposed to deal with
12 today, I believe.

13 DR. HORLOCKER: Dr. Smiley?

14 DR. SMILEY: Yes, well, the problem, and
15 I know you know this, and the problem of course is,
16 that's not exactly the question, because I think we
17 all know that in clinically-used doses, the vast,
18 vast, vast majority of the times, neither of these
19 drugs is dangerous at all.

20 The problem is in that rare instance where
21 you get a intravascular or some other abnormal
22 absorption of the drug, mostly it's intravascular, so

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1 that that's what -- I mean, I know, again, I'm stating
2 the obvious, but it's important to get that out there.

3 It's not -- the difficulty the Sponsors
4 have is that even at clinically-used doses, it's hard
5 to show differences in toxicity because we don't have
6 surrogate endpoints for the V-tach, V-fib arrests that
7 you see with the massive overdoses.

8 DR. REVES: I would comment on the three
9 cases that we do have of inadvertent intravenous
10 absorption of the drug. It does -- two happen to be
11 bupivacaine and one levo, and it appeared to my
12 looking at it -- not having gone over the Case Report
13 Forms or seen the EKGs or any of the other things --
14 it did appear in the three cases, that is, n = 1 for
15 the study drug, that it seemed to be a little less
16 toxic than the two others but, you know, what can you
17 decide on three cases? But we do have those three to
18 kind of look at.

19 DR. HORLOCKER: Any other questions? Yes,
20 Dr. Savarese?

21 DR. SAVARESE: Yes, I think that's
22 important. I'm glad that Dr. Reves made that

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1 observation, because I was thinking the same thing.
2 I think we do have to pay some attention to that, that
3 there were to bupivacaine cases, where there was a
4 severe reaction, and where there had to be a
5 resuscitation.

6 Whereas, with levo, there was -- it's only
7 one case, but that patient really didn't require
8 anything except a little barbiturate, right? Is that
9 correct? Yes?

10 I just wanted to go back to the potency
11 comparison. Dr. Gennery, in that paper from -- now
12 we're talking 25 years ago -- if the potency
13 comparison is as you say -- I'm not familiar with the
14 paper at all, but if that paper shows identical
15 potency in humans -- is that correct?

16 DR. GENNERY: Yes, it was. Volunteers.

17 DR. SAVARESE: In humans? In human
18 volunteers of an adequate number, then I think we can
19 start to be content that the potencies of all three of
20 these mixtures of isomers are --

21 DR. GENNERY: Can I -- Can I just --

22 DR. SAVARESE: Sure.

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1 DR. GENNERLY: -- bring two other bits of
2 data to your attention --

3 DR. SAVARESE: Sure.

4 DR. GENNERLY: -- which are in the NDA.

5 DR. SAVARESE: Sure.

6 DR. GENNERLY: One is an ulnar nerve block
7 study, where we compared three doses of
8 levobupivacaine against a standard dose of
9 bupivacaine. And demonstrated equal efficacy, equal
10 potency.

11 And secondly, is an MLAC study, which is
12 a rather complex algorithm for trying to determine
13 minimum local analgesia concentration required to
14 relieve pain in first stage of labor. And we have got
15 a slide of that which Dr. Graeme McLeod can talk to.

16 DR. SAVARESE: Can I just ask you, when
17 was that ulnar nerve block study done? Was that a
18 recent study?

19 DR. GENNERLY: Three years ago.

20 DR. SAVARESE: Okay.

21 DR. GENNERLY: The MCLAC Study includes two
22 comparisons; one where we -- which was ours --

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1 comparing levobupivacaine and bupivacaine, and one
2 from Dr. Linda Pauley in the Mayo Clinic, looking at
3 ropivacaine and bupivacaine.

4 DR. McLEOD: Good afternoon. Dr. Graeme
5 McLeod, I'm a consulting anesthetist from Langwell's
6 Hospital in Dundee, Scotland. I am a clinical
7 investigator with Chiroscience.

8 What I would like to do is address this
9 issue regarding potency on a weight to volume basis,
10 and there has been, as has been indicated by Dr.
11 Gennery, a methodology used by several groups, used to
12 indicate the relative potency between these drugs.

13 And we've only got the one slide here, but
14 I'm just going to indicate the methodology. In fact,
15 this is a double-blind, sequential allocation method,
16 based on a methodology devised by Dixon and Massey.

17 It's a multiclinical algorithm, which was
18 created whereby a standard 20 ml volume is given to
19 patients and the dose of drug is dependent on the
20 response of the previous patient.

21 In other words, the previous patient that
22 has successful analgesia, as indicated by an MLAC

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1 score of less than 10 ml after 30 minutes, then the
2 concentration is reduced by 0.1%.

3 On the other hand, if the previous patient
4 had had unsuccessful analgesia, then the subsequent
5 dose to the following patient was subsequently
6 increased by 0.1%, and that created what has been
7 described by the studiers as a free floating
8 mechanism. What it does is it derives effectively an
9 ED-50 and an ED-95 for both drugs.

10 Now, what this indicates on the left side
11 are the results by Lyons and Columnatal from Leeks in
12 England, and what they have found is that the ED-50,
13 the MLAC ED-50 for bupivacaine was .081%, and for
14 levobupivacaine was .083%, giving a relative potency
15 of .98.

16 And I have a graph in my laptop, if you
17 want to look at it, that actually shows a dose
18 response curve. And the dose response curve, goes
19 from .06 to .12%, and in fact, the dose response curve
20 is similar for both drugs. And more or less parallel.

21 Unfortunately, this study, the numbers
22 were small, only 60 patients were ever treated, and

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1 the confidence intervals were rather large, and
2 therefore, the investigators could not see with
3 confidence that there was no difference between the
4 drugs.

5 And the study on the right, and I have to
6 talk about it, it's on the slide, is a comparison by
7 Linda Pauley using the same methodology, only in
8 patients in whom had, were dilated up to 7 cm, and
9 different end parameters were used; nevertheless, it
10 does indicate a potency difference between ropivacaine
11 and bupivacaine of .65, with an MLAC of bupivacaine in
12 this Study of .093%, and for ropivacaine, of .156%.

13 DR. HORLOCKER: Yes, sir.

14 DR. PERMUTT: Dr. McLeod, I believe you
15 said that confidence intervals for the relative
16 potency were rather wide. Were they as wide as, say,
17 30%?

18 DR. McLEOD: No, they were about 15 to
19 20%.

20 DR. TOBIN: To follow-up on Dr. Savarese's
21 question, I think the idea of understanding
22 equipotency is important, and maybe we have sufficient

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1 data, possibly not.

2 What I am more interested in is the
3 illustration on the last slide that Dr. Permutt put
4 up, which really showed what I think is the crux issue
5 here, and it responds to what Sue said earlier, too.

6 What is the incidence of the
7 cardiotoxicity at the efficacious dose, and then,
8 follow-up with more data that we have discussed a
9 little bit earlier this morning, of what is the
10 resuscitateability of those very toxic or dangerous
11 effects?

12 So, Dr. Permutt, if we go back to your
13 last overhead, where you have the four curves, I think
14 that's the best graphic illustration of the crux of
15 what we're all asking for.

16 DR. SAVARESE: We could call that Dr.
17 Permutt's last permutation. You've probably heard
18 that before, a bunch of times.

19 DR. TOBIN: Once or twice. Assuming with
20 the group of two curves on the left, that we are at
21 100% efficacy of the dose, which is what most of our
22 clinical data suggests, or that we are very close to

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1 that point, where those two curves converge, what I am
2 most interested in is where are the beginning of the
3 two curves to the right?

4 And are they immediately beginning
5 underneath the convergent points of the two curves to
6 the left, or are they actually potentially further to
7 the left on this graph, compared with their current
8 location?

9 And then, the separation between the toxic
10 curves may have a great deal, greater ramification,
11 but if the two of them both have the left foot of
12 their curves exactly at the 100% efficacious dose, or
13 so close to it, would it really matter if these two
14 drugs are equally potent or not?

15 And I think it is the numerator over the
16 denominator that becomes critical here, and
17 unfortunately, without a power of 100,000 patients
18 enrolled in a study, the Sponsor may never be able to
19 give us exact comparisons of numerator over
20 denominator, to our satisfaction.

21 But more concerningly, is the outcome of
22 what happens in those toxic events, and I think to

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1 address the potential resuscitateability in the whole
2 animal model is critical for us to make a
3 determination if one drug is actually safer than the
4 other.

5 DR. PERMUTT: Just to clarify, I did not
6 mean to suggest -- I crammed them onto the slide, but
7 I did not mean to suggest that toxicity of either drug
8 was beginning at approximately the dose as where we
9 were getting complete efficacy.

10 As someone said earlier, bupivacaine has
11 in general fairly wide therapeutic index, and I didn't
12 mean to suggest otherwise, only to question whether
13 levobupivacaine has an even wider one.

14 DR. HORLOCKER: Dr. Savarese?

15 DR. SAVARESE: Well, let me just ask this
16 question. As a Panel, possibly where -- are we
17 possibly satisfied by now that the local anesthetic
18 potency of levo versus racemic bupivacaine is the
19 same?

20 If we can assume that, then the key
21 question is, what is the relative toxicity data that
22 we have got from the animal studies, and I would like

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1 to hear Dr. Mather's data again, and Dr. Nimmo's data
2 again on the human intravenous toxicity, because those
3 are the two key questions, I think.

4 DR. ROBERTS: May I make a point while we
5 wait for the presentation? I would like to reiterate
6 what Dr. Carlisle says. I think that the only way to
7 really answer your question is to conduct a study in
8 which equipotent doses were analyzed with respect to
9 the toxicity obtained at acceptable doses.

10 I think that we have seen evidence of
11 toxicity demonstrated at acceptable doses. We have
12 seen anything from bradycardia and hypertension to
13 asystole occurring.

14 So, I think if we had a study in which we
15 analyzed both simultaneously, we may be able to answer
16 that question.

17 DR. SAVARESE: I think one of the things
18 that we are concerned about here is that -- my opinion
19 is, is that the two drugs seem to give the same kind
20 of clinical performance. And that's just clinical
21 performance.

22 You're interested in safety here. We

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1 don't see a difference in properly performed clinical
2 comparisons, of a safety difference. But that's just,
3 as we're saying, the lower end of the toxicity curve,
4 the very lowest part of it. And what we are most
5 concerned about is what happens if somebody gets an
6 accidental overdose of one kind or another.

7 And that's just not going to be possible
8 to perform clinical studies of that sort. However,
9 the other thing is that, I don't agree with Dr.
10 Roberts. I'm sorry to disagree with you, but I think
11 that a lot of the stuff that we are seeing here is
12 simply the side effects of the anesthetic drug, and it
13 does not include -- or does not indicate a toxicity.

14 I hope that's not what you meant. Were
15 you thinking that this was actually a symptom of
16 toxicity of drug?

17 DR. ROBERTS: What I'm thinking is, we
18 have not seen enough evidence to prove that it is not.
19 Or that it is.

20 DR. SAVARESE: Well, again, I think we can
21 -- I can, anyway, I'd like to ask the rest of the
22 Panel to think about this. I can explain most of

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1 these symptoms that were seen in the testing of the
2 drug as just the consequences of a high block, or a
3 relative overdose, or an error in judgment in dosage
4 on the part of the investigator, or just unfamiliarity
5 with the drug.

6 DR. JEAN: Perhaps in order to help this
7 doctor over there, I would like to ask the Sponsor if
8 you have the slide for peak study that you have a
9 curve showing QRS effects?

10 If we use increased QRS interval as one of
11 the cardiotoxic parameters, I would like to show you
12 the shape of the curve. The separation between
13 bupivacaine and levobupivacaine.

14 DR. GRISTWOOD: Okay, these are the data
15 I showed earlier from the Reitz and Morrison pig
16 intra-coronary artery infusion study, showing the
17 increase in QRS duration times the dose of drug
18 administered.

19 And this is the curve for bupivacaine, and
20 the curve for levobupivacaine, here.

21 And making assessments of the difference
22 in effects on the QRS duration, there was a 25%

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1 difference at this level, with a 40 msec increase, and
2 there's a 47% difference at the level of 90 msec
3 increase in QRS duration. Does that answer your
4 question?

5 DR. JEAN: Yes. Would that help him?

6 DR. TOBIN: I'm sorry, it doesn't help as
7 much as I would like, because this is obviously the
8 drug delivery into the coronary artery, causing this,
9 and as Dr. Savarese says, it's the unintentional
10 delivery of a small amount of drug to the
11 intravascular system that is probably responsible for
12 the side effects we are seeing.

13 Although the data is helpful, somewhat,
14 I'm not sure I can quantitate it without knowing
15 confidently that they are indeed equally potent. But
16 just as importantly is, what is the outcome of a
17 prolonged QRS of an extra 90 msec?

18 That in and of itself may not be
19 sufficient to cause clinical symptoms. It frequently
20 does. But, if these are not non-resuscitateable
21 rhythms, then this is preliminary data and we still
22 need to go on to resuscitateability from the

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1 catastrophic cardiovascular collapse.

2 DR. SAVARESE: Could we also see Dr. --
3 Madame Chairman, if it's okay with you --

4 DR. HORLOCKER: It's fine.

5 DR. SAVARESE: -- Dr. Mather's comparative
6 data, and then Dr. Nimmo's comparative data, because
7 these are also comparative toxicity data, which are
8 key. Just one or two slides which you think are
9 important.

10 DR. SMILEY: John, can I just -- I get the
11 sense that we are almost of a consensus; that the
12 human data, for the reasons we have talked about, is
13 not that useful for us. So, I'm not quite sure why
14 you would want to see that again.

15 I thought we had more or less come to a
16 consensus that, because there is no surrogate
17 endpoint, the human, sort of subtoxic dose data just
18 won't let us make any conclusions about the human, so
19 I'm not -- what are you looking for?

20 DR. SAVARESE: Well, I'm looking for
21 Nimmo's data at the highest dosage levels of each --
22 he's comparing milligram for milligram of the

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1 comparative symptomatology in the two sets of
2 volunteers.

3 I think they were the same people, wasn't
4 this a crossover study? Is that right, Walter?

5 DR. NIMMO: The first study was a
6 crossover study. The second one I presented was a
7 parallel group study. But in the first one, you are
8 right, they were crossed over.

9 DR. SAVARESE: Okay, so I mean the
10 question is, just let's see that data one more time.

11 DR. HORLOCKER: The healthy volunteer data
12 where they had delivered an infusion --

13 DR. SAVARESE: Yes.

14 DR. HORLOCKER: -- and stopped at the time
15 of first CNS toxicity?

16 DR. SAVARESE: Yes. I think that --

17 DR. HORLOCKER: Do you have that slide?

18 DR. NIMMO: Yes.

19 DR. HORLOCKER: I actually have a little
20 bit of problems with the human data, because the CNS
21 toxicity occurred at the same, or not a statistically
22 different, milligram difference, so that they occurred

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1 at the same time; they really weren't that different;
2 and within our 50 mg intravenous dose.

3 So, we haven't been able to really show
4 that humans respond differently to levobupivacaine
5 versus bupivacaine, so I agree.

6 DR. SAVARESE: That's my point. Not that
7 the experiment is bad, but that I really think that
8 our consensus is pretty clear on this one, that there
9 is just not enough human toxicity data to make much
10 conclusion with or without potency data. In the
11 human.

12 DR. HORLOCKER: And the good news of
13 course is that you could deliver 50 mg intravenously
14 and not even seize; they only had, that was over
15 several minutes' time, but that is reassuring at least
16 for both local anesthetics.

17 DR. NIMMO: These are the data on stroke
18 index, acceleration index, and the first study, which
19 was the crossover study, and 14 volunteers, all
20 volunteers experienced CNS effects; remember, the dose
21 was stopped only when CNS effects occurred, except in
22 the one volunteer who got to 150 mg of levobupivacaine

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1 with no CNS effects.

2 DR. DiMARCO: Can I ask a question about
3 this study? Your methods say that you had two people
4 drop out because of a greater than 20% fall in cardiac
5 output. Those are the people I'm actually most
6 interested in.

7 Why did you have people, you know, why
8 aren't they counted? That's a, that's the toxicity
9 we're looking for, not these trivial changes in the
10 range of normal.

11 DR. NIMMO: Correct. And these changes
12 are in the remaining 12.

13 DR. DiMARCO: So, what happened in -- you
14 know, can you describe what happened in those two
15 people on bupivacaine, and one on L-bupivacaine who
16 had a greater than 20% fall?

17 DR. NIMMO: The study was a first infusion
18 administration to man study for levobupivacaine, and
19 so we were concerned that what might happen when
20 levobupivacaine was infused for the first time to
21 human beings, and the BoMed was being used as an
22 indicator of safety.

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1 So that whenever there was a sustained in
2 cardiac index, over two observations, then we wouldn't
3 dose the patients again, the other volunteers again,
4 rather.

5 DR. DiMARCO: Then, the other question I
6 had was --

7 DR. NIMMO: They recovered rapidly, you
8 see.

9 DR. DiMARCO: The other question is, when
10 you did your testing with lidocaine -- I'm not an
11 anesthesiologist -- when you did your testing with
12 lidocaine, you went to what you thought was the onset
13 of CNS toxicity.

14 Did you examine any of these measurements
15 in those individuals, to see that what -- we usually
16 think that lidocaine is relatively cardio-safe, did
17 you look, are any of these changes just associated
18 with the CNS toxicity, and unrelated to direct effects
19 on the heart?

20 DR. NIMMO: In the lidocaine group, we
21 only made safety observations, we did not measure --

22 DR. DiMARCO: So, you don't have any

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1 measurements.

2 DR. NIMMO: No.

3 DR. HORLOCKER: Dr. Savarese, did you want
4 additional information?

5 DR. NIMMO: Well, we are going to present
6 the EKG results.

7 DR. SAVARESE: Yes, but again, the drop-
8 outs from the study, they were dropped because they
9 became hypotensive?

10 DR. SAVARESE: Their cardiac index dropped
11 and was sustained for more than a minute.

12 DR. SAVARESE: Yes, and there were two
13 drop-outs in the bupivacaine side, and one on the
14 levobupivacaine side?

15 DR. NIMMO: No, there was one in each.

16 DR. SAVARESE: Pardon me? One in each?
17 Okay. Go ahead, yes. Now you're going to give us the
18 CNS data?

19 DR. NIMMO: Okay, in this study, remember,
20 all volunteers had CNS symptoms, and these are the 12
21 who remained in the study, they had both infusions,
22 and one can make the comparison in the stroke index,

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1 acceleration index, between the two groups.

2 And there was a significant difference
3 between the two groups with respect to the fall in
4 stroke index, of which there are almost 11 ml/m²,
5 compared with 3.3 in the levo group.

6 And acceleration index, a reduction of
7 0.18 per second per second, compared with 0.06 for
8 baseline in the levobupivacaine group.

9 That is the same data shown graphically.
10 And then this group of volunteers. The PR interval
11 was significantly prolonged in the bupivacaine group,
12 but there was no significant increase from pre-dose in
13 the levo group, although let me say, there was no
14 difference between the two groups.

15 And also in this study, in the 12
16 volunteers, there was a significant increase in QTc
17 only in the bupivacaine group, and not in the
18 levobupivacaine group. The differences were not
19 great, and there was no difference between the two
20 groups here.

21 DR. DiMARCO: Yes, I mean, if you look at
22 the deltas. You know, it's 22 +/-35 and 21 +/- 31.

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1 It's hard for me to say that there's -- you know, to
2 make anything about that. The magnitude of the delta
3 is the same, starting from the same baseline. Maybe
4 your statistics are different, but -- it's hard to say
5 anything about that.

6 DR. NIMMO: And you remember, the next
7 study, Dr. Savarese, was in 22 healthy volunteers, and
8 they all had bupivacaine until the same side effects,
9 and the dose range was 30 to 120.

10 They were then allocated randomly to a
11 double-blind, parallel group study, to receive
12 levobupivacaine or bupivacaine. And more intensive
13 EKG observations were made.

14 And in this group, everybody in the
15 bupivacaine group got CNS effects, but only 6 of the
16 11 in the levobupivacaine group got CNS effects,
17 because the dose was cut from the previous bupivacaine
18 infusion.

19 And here are the data from this study.
20 The doses did not differ significantly. The Cmaxs did
21 not differ significantly, and they were similar to the
22 previous study.

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1 The only statistically significant
2 observation was in the prolongation of the QTc
3 interval, in the volunteers who received more than 75
4 mg of test drug.

5 DR. SMILEY: There's obviously a typo on
6 that slide, isn't there? Is it -- is the 12 should be
7 a 2, or the 17 should be a 7? Because there are only
8 19 patients in the study, right?

9 DR. NIMMO: There were 22 patients in the
10 study, and these are the standard deviations in the
11 brackets.

12 DR. DiMARCO: Those aren't numbers, those
13 are --

14 DR. SMILEY: Those aren't numbers?

15 DR. DiMARCO: Those aren't numbers of
16 patients, those are maximum increases.

17 DR. NIMMO: These are the standard
18 deviations in the brackets.

19 DR. DiMARCO: Those are milliseconds.

20 DR. SMILEY: So, how many numbers in each
21 groups?

22 DR. NIMMO: There were seven in this group

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1 and four, seven and four. And between these two
2 groups, there was no overlap at all. All four in this
3 group had a smaller QTc increase, than in this group.

4 DR. GENNERY: Is that sufficient, John, to
5 see the data?

6 DR. SAVARESE: That's the cardiovascular
7 data, but I think your point was that -- I mean, I
8 myself, personally, am fairly convinced about the
9 differences, particularly with respect to myocardial
10 contractility between the two that you showed, those
11 graphic differences. They are certainly -- you can't
12 ignore them.

13 But you said that those two groups of
14 people each received enough of either bupivacaine or
15 levobupivacaine, one or the other, to get to CNS
16 symptomatology?

17 DR. NIMMO: Yes, in the first study, yes.

18 DR. SAVARESE: In the first study. In
19 this study, all of the bupivacaine volunteers got to
20 CNS symptomatology, and only half of the levo people?

21 DR. NIMMO: Yes.

22 DR. SAVARESE: Well, I think that's

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1 important, too.

2 DR. SMILEY: Well, but that also could be
3 explained by 20% lower potency, and they just missed
4 the -- remember, you're going right to the borderline
5 of toxicity with bupivacaine. If levo happened to be
6 a little less potent, that's exactly the results you'd
7 see.

8 You would see fewer of them reaching CNS
9 toxicity on the second time.

10 DR. SAVARESE: Yes. So, I agree with you.
11 Potency is key question and this is all under the
12 assumption that they are the same potency.

13 I think we're going to need maybe a little
14 bit more reassurance of potency identity, in order to
15 shore up this data.

16 I also would like to ask Dr. Mather to go
17 over his, because that -- your slide of convulsant
18 dose -- I'm specifically thinking of that one, where
19 there is a clear separation of convulsant doses.
20 Could you just go over that data and explain that to
21 us again?

22 DR. MATHER: We should have the summary

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1 slide that puts together the convulsant doses with
2 respect to the fatal doses. I think this might help
3 clarify issues as well.

4 The point about the slide is that we are
5 looking at the main convulsant dose of levobupivacaine
6 and bupivacaine, and seeing the separation between
7 them.

8 At the same time, you can see the mean
9 fatal dose. And the ratio then exhibited between the
10 convulsant and the fatal doses, is in the order of
11 three for levobupivacaine, compared to two for
12 bupivacaine.

13 I think this is an important issue in
14 itself. There has been some controversy in the
15 literature of which you may be aware, of the role of
16 the central nervous system in inducing arrhythmias,
17 and I think this is a significant issue in its own
18 right.

19 There is no doubt that arrhythmias can be
20 induced, stereo-selectively, and it's been
21 demonstrated with the R and S enantiomers of
22 bupivacaine. The stereo-selectivity plays a role with

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1 injection of these agents. So, the role of the
2 central nervous system and the cardiovascular system
3 can't be underestimated in this case.

4 So, the point about this is, I think, that
5 a margin of safety in the central nervous system,
6 which are convulsant levels, also may be conveying a
7 margin of safety in the cardiovascular system.

8 I wouldn't want to speculate too loudly or
9 to too wide a public audience at the moment about the
10 mechanisms involved in this, but a case has come to
11 mind of the epileptic patients who have sudden cardiac
12 death, etcetera.

13 But, placing the simple interpretation of
14 the numbers. There is a margin of safety in both
15 issues there, central nervous system and
16 cardiovascular death. Does that sort of clarify the
17 point you wanted?

18 DR. SAVARESE: There's a specific slide
19 you showed. It's a graphic comparison of convulsant
20 dose after IV infusion of bupivacaine versus
21 levobupivacaine. And there is a clear separation of
22 the two, and I think we should look at that again.

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1 DR. HORLOCKER: Dr. Mather, on your
2 previous slide for fatal dose, is that to mean the
3 cardiac collapse? So, essentially, you were
4 calculating the cardiac collapse over CNS collapse
5 ratio that we're used to discussing.

6 DR. MATHER: They were Dr. Santos' data
7 and, yes.

8 DR. REVES: It's a fatal arrhythmia,
9 right?

10 DR. MATHER: These are convulsant doses,
11 per se. Is this the data you wanted to --

12 DR. SAVARESE: Yes, that's the one I
13 wanted to look at.

14 DR. MATHER: Right. There are individual
15 animals, and then the mean and the 95% confidence
16 intervals of the group means.

17 DR. HORLOCKER: Again, are these
18 statistically significant?

19 DR. MATHER: Yes, they are.

20 DR. SAVARESE: I think, looking at the
21 individual data on the left is what strikes me, is
22 that there is absolutely no overlap even of

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1 individuals there.

2 DR. MATHER: Well, there is one
3 overlapping value, but, yes --

4 DR. SAVARESE: Oh, the lowest one on the -

5 -

6 DR. MATHER: Yes, the lowest one. There
7 is also one very low one in the bupivacaine --

8 DR. SAVARESE: Right. Right.

9 DR. WATCHA: I think the confidence
10 intervals on the right show it much clearer.

11 DR. MATHER: Again, the failure of the
12 confidence intervals to overlap I think is impressive.
13 Can I expand on that any further for you?

14 DR. SAVARESE: Well, you've had loads of
15 experience doing studies like this.

16 DR. MATHER: Yes, I have.

17 DR. SAVARESE: Could you put these into a
18 context with other local anesthetics, for example?

19 DR. GENNERËY: Indeed, I could. The values
20 for lidocaine will be approximately 300 mg. The
21 values for ropivacaine will be almost identical of
22 those for levobupivacaine. Slightly higher, but

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1 almost identical on the upper edge of the
2 levobupivacaine.

3 When it comes to the fatalities, then the
4 same order pertains. So, lidocaine, 350 would be a
5 round number. Ropivacaine, approximately 140 would be
6 in that range, going down as low as 100. Something in
7 that range.

8 So, the bupivacaine in all cases is the
9 lowest on the ranking of those four commonly used
10 local anesthetics.

11 DR. SMILEY: Can I ask for clarification
12 on that? Just based on the numbers? Dr. Mather, on
13 the numbers you just threw out there, would imply that
14 in fact as clinically used, both levobupivacaine and
15 ropivacaine would be, quote unquote, safer than
16 lidocaine. Because therapeutically, lidocaine is used
17 at four times the dose. And you're talking about
18 ratios of 2, 2.5 to 1.

19 DR. NIMMO: The lethal dose on the same
20 scale for lidocaine is approximately 1500 mg --

21 DR. SMILEY: Oh, the lethal. No, this is
22 just convulsant dose. Okay. Fine. But as far as

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1 seizures, though, that's all you're concerned about.

2 DR. NIMMO: As far as seizures, yes, it's
3 interesting, and again, if you look at the dose for
4 lethality compared to that for seizures, the value for
5 lidocaine is slightly lower that you would predict on
6 the potency ratio.

7 In the case of fatality, the value for
8 bupivacaine is about twice as toxic as you would
9 predict on the basis of that.

10 DR. SAVARESE: I think, just to further
11 question you about this, that the remark you just
12 made, plus something that you may have implied or even
13 come out and stated during your presentation was that
14 you think there may be a kinetic difference the two,
15 maybe explaining some of the CNS differences that you
16 see? Is that true?

17 DR. NIMMO: I wouldn't --

18 DR. SAVARESE: Could you go ahead and talk
19 about that some more?

20 DR. NIMMO: I could talk about this some
21 more, certainly. I've done some fairly subtle
22 pharmacokinetics by way of mass balance calculations

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1 of the amount of drug and its flux across the blood-
2 brain barrier, and into the myocardium.

3 It turns out that there is no discernible
4 difference between the R and S enantiomer of
5 bupivacaine, and their rate of uptake through the
6 blood-brain barrier, into the brain.

7 There is a subtle difference, a small
8 difference, with respect to the heart. And in fact,
9 there is actually slightly less S enantiomer of
10 racemic bupivacaine gets into the heart at the peak
11 effect, compared to the R enantiomer.

12 The mean value is approximately 92% with
13 a confidence interval of about 4 or 5%. So, it's
14 statistically significant. It's small, but it's all
15 in the same direction. It's all saying, lower
16 intrinsic toxicity on the heart, and a slightly lesser
17 uptake into the heart.

18 Small difference. Statistically
19 significant. Subtle, but all in the same direction.

20 DR. HORLOCKER: Yes, sir. This is the
21 last question, I'll break for lunch.

22 DR. GOHEER: My question is to Professor

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1 Mather. You have completed the intra-coronary artery
2 infusion in the sheep.

3 DR. MATHER: Yes, I have.

4 DR. GOHEER: Would you like to say
5 something about this?

6 DR. MATHER: I can't find my crib notes,
7 I'm afraid, so I will talk from memory. The story is
8 that we infused doses into the coronary artery in a
9 parallel group, randomized, blinded manner, in which
10 the coding was broken after the analyses had taken
11 place.

12 We started with the injections at 2.5
13 nominal mg and increased by 2.5 nominal mg until
14 either a maximum of 12.5 mg, or a lethal outcome
15 ensued.

16 The animals were prepared in exactly the
17 same way for exquisite measurement of cardiac
18 dynamics. The injection was made into the bifurcation
19 of the left anterior descending of the left circumflex
20 coronary arteries, in a retrograde manner, to get the
21 maximum degree of mixing of drug, as it was injected.

22 The broad outcome was that injections of

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1 levobupivacaine, five out of seven of the animals in
2 the cohort died during the studies. The bupivacaine,
3 four out of six died. For ropivacaine which was
4 included as a comparative, four out of six died.

5 The mean lethal dose for all of them was
6 almost exactly 22 micromolars with a small standard
7 deviation and there was no statistical difference
8 between the three values of the lethal doses, nor of
9 the frequency of deaths occurring in the series.

10 The results were surprising, and contrast
11 somewhat with the differences with intravenous dosing.
12 The differences between intravenous dosing where much
13 larger differences between the potencies of the drugs
14 were revealed.

15 My hypothesis for this, and I draw the
16 attention to the word, hypothesis is, that the
17 greatest difference between the drugs is in the
18 central nervous system activity, and I believe that
19 the activity of the central nervous system acts to
20 coincide with the direct effects of the drugs on the
21 heart to give a greater bias.

22 So, I believe in my preparation, which is

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1 the only preparation of a single dose that is
2 performed in a conscious animal, the intrinsic
3 differences in cardiac toxicity between the drugs is
4 much smaller than one would predict from the
5 intravenous toxicity.

6 And the principle difference is revealed
7 by the manifestation of the central nervous system
8 effects feeding back onto the heart.

9 DR. HORLOCKER: Thank you. We will
10 adjourn for the morning session now and reconvene at
11 2:00.

12 (Whereupon, at 1:04 p.m., the Advisory
13 Committee Meeting was recessed, to be
14 reconvened later the same afternoon.)
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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (2:00 p.m.)

3 Committee Discussion

4 DR. HORLOCKER: If everyone would take
5 their seats, we will start the afternoon session. I
6 believe we have already covered a significant part of
7 the discussion earlier today, but what I would like to
8 again remind the Advisory Committee on, are the two
9 questions that the FDA has asked us to address.

10 And these are, specifically, has the
11 Sponsor adequately evaluated levobupivacaine's
12 potential for cardiac toxicity at the labeled dose,
13 and if not, what further studies are needed?

14 Secondly, should the boxed warning that
15 currently exists in the bupivacaine label be applied
16 to this product?

17 Now, what I would like to do is throw a
18 real wrench in the whole discussion here, and let's
19 discussion number two first, because when the black
20 boxed warning was placed in 1983 around bupivacaine,
21 anesthesia practice was much different than it is
22 today. Specifically, we don't inject the whole dose

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1 at once, we use a test dose. We inject incrementally
2 and aspirate incrementally.

3 And so we don't see the same problem with
4 racemic bupivacaine that was reported in Albright's
5 Study. And there have been others on this Advisory
6 Committee Panel that met in March of 1997, and those
7 that discussed ropivacaine in 1996 that have said,
8 perhaps we don't need the boxed label warning on
9 bupivacaine.

10 Now, if we don't need the boxed label
11 warning on bupivacaine, then certainly, regardless of
12 whether the potency of levobupivacaine and bupivacaine
13 are identical or not, it wouldn't matter and we
14 wouldn't need the boxed label warning on
15 levobupivacaine or bupivacaine.

16 So, I would actually like the Committee to
17 address this issue first. Would we like to rescind
18 the black boxed warning on bupivacaine? Dr. Smiley?

19 DR. SMILEY: Do we -- I hate to say this,
20 but do we have a copy of that black boxed warning to
21 put up there, because as I remember -- I mean, I've
22 read it many times, but before --

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1 DR. HORLOCKER: In fact, we have one in
2 our packet and -- does anybody have an overhead?

3 DR. SMILEY: -- because the -- the point
4 I wanted to make is that, while we would all agree
5 that bupivacaine is a potentially dangerous drug. I
6 agree with you about changes in practice, at least in
7 epidural anesthesia, for the most -- at least at
8 academic centers.

9 But, I think that if there were -- if one
10 were to write the black box warning now, it would be
11 so different than what is in that black box, that I
12 think that, I believe that that black box is not
13 really relevant to current practice, and doesn't
14 conform with current scientific information, either.

15 Whether a special warning for this class
16 of drugs is needed, is a slightly different question,
17 but if you were asking me whether that black box would
18 be put on bupivacaine now, the answer is almost
19 certainly, no, because it really is not in conformance
20 to what I understand to be the problems with using
21 these drugs as anesthesiologists.

22 DR. HORLOCKER: In fact, what I would

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1 suggest is that we actually look at the labeling for
2 bupivacaine and also for the way the warning was
3 worded for ropivacaine when it was approved in 1996,
4 and that there still are some very strong statements,
5 all in capital letters, that say that this is a drug
6 not to be used at high concentrations in obstetrics
7 and under certain circumstances.

8 And as you are saying, perhaps this is the
9 way the warning would be worded, should it be
10 wordsmithed today.

11 So, if we could get copies of those two
12 labels, I think that would help us.

13 DR. ASHBURN: They're in the big black --

14 DR. HORLOCKER: Right. They're also in
15 the -- at the very beginning of the blue -- you can
16 see that the black box warning pertains to 0.075%
17 bupivacaine in obstetrical use. It has no other real
18 applications as pertaining to a surgical or
19 pediatrics, or other applications of regional
20 anesthesia.

21 And again, this label states what the
22 facts were at the time. That there had been cardiac

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1 arrests and difficult resuscitations and deaths that
2 occurred in patients that have received, presumably
3 large intravascular injections of 0.75% of
4 bupivacaine.

5 Could I have the ropivacaine label, the
6 beginning of it, where it discusses the use in
7 obstetrics?

8 DR. ASHBURN: It's the last tab in the
9 large blue --

10 MS. REEDY: We don't have that on a slide,
11 but it's the 1996 tab in the blue briefing package.

12 DR. HORLOCKER: I can read the beginning
13 of it. This is under the Noropin labeling, under
14 warnings. And in capital letters, the warning is
15 stated, "For Cesarian Section, the 5 mg/ml solution in
16 doses up to 150 mg is recommended. As with all local
17 anesthetics, Noropin should be administered in
18 incremental doses, since Noropin should not be
19 injected rapidly in large doses, it is not recommended
20 for emergency situations where a fast onset of
21 surgical anesthesia is necessary.

22 "Historically, patients reported to have

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1 a high risk for cardiac arrhythmias, cardiac
2 circulatory arrest, and death when ropivacaine was
3 inadvertently rapidly injected intravenously."

4 So, if you recall from the transcript of
5 the ropivacaine discussions, this was a very difficult
6 decision for the Advisory Committee to make at this
7 time. This was their compromise, to still state the
8 facts as they were historically related to
9 bupivacaine, and during the ropivacaine discussions,
10 as with levobupivacaine, had no true data showing
11 whether these patients would still be at high risk or
12 not, and so they wanted to put the historical
13 perspective in the label, and just state the facts as
14 they existed then.

15 Dr. Smiley, did you want to?

16 DR. SMILEY: Well, I think that is a much
17 fairer statement of the issues. None of us would
18 question that local anesthetics are dangerous, and that
19 some are a little more than others.

20 So, that would probably, again, starting
21 from scratch, I think that would be we would be at.
22 I do understand, or I am starting to understand, some

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1 of the implications of removing black boxes, and
2 having very similar drugs, and none of us would argue
3 that levobupivacaine is fundamentally a very different
4 drug from bupivacaine.

5 Not having a black box on one, having it
6 on the other is slightly different than if this was a
7 brand new drug class. I'll stop there for now.

8 DR. HORLOCKER: I'll interject then, also,
9 that, if we do not place the black box warning on
10 levobupivacaine, we will have to, more than likely,
11 evaluate or reassess whether we want to remove it from
12 bupivacaine, also, because they will -- the
13 manufacturers no doubt will submit a --

14 So, this really is a timely discussion,
15 that we will have at one point in time or another.

16 DR. SMILEY: But there's a big difference
17 between, as I understand it, between putting a black
18 box on something, and simply not having it as an
19 indicated use.

20 DR. HORLOCKER: Correct.

21 DR. SMILEY: I mean, none of us are
22 claiming that it's indicated to use 0.75% for Cesarian

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1 Section, or frankly where I think the next bupivacaine
2 death will come will not be in C Sections, where
3 incremental injections are done, but rather in nerve
4 blocks, where that's not as possible, when there's
5 just a needle sitting there.

6 So, that's my fundamental objection to the
7 black box warning, is it's not warning about the right
8 thing. The problem is, giving any patient a sudden,
9 large dose of any of these drugs, and yes, maybe
10 bupivacaine is a little worse, so it actually has this
11 incredibly powerful message about slightly the wrong
12 subject.

13 DR. HORLOCKER: Could I get a member of
14 the FDA to actually discuss with us, what the medical
15 legal implications of the black box labeling is, and
16 also, the warnings, the way they are worded; for
17 example, with the ropivacaine drug? What do they
18 mean, what do they infer?

19 DR. MCCORMICK: I don't think it's
20 actually written in stone or in the regulations, you
21 know, what the medical legal implications are.
22 Certainly, if something is contraindicated in the

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1 warning section, whether it's in a box warning, at the
2 front of the label, or in the warning section of the
3 label, the Sponsor certainly cannot advertise, promote
4 its use.

5 It's really up to a practitioner to decide
6 how he or she is going to use a product. I can't
7 specifically speak to the medical legal implications,
8 because that's really outside of our realm.

9 I would think that a practitioner would be
10 taking on a great risk, certainly if he or she had a
11 complication with a product, if it was specifically
12 contraindicated in the warning section of the label.

13 DR. HORLOCKER: Well, as I understand it,
14 the Sponsor is not seeking 0.75% levobupivacaine for
15 use in obstetrics, correct?

16 DR. GENNERY: That's correct. We've done
17 those studies and we're not asking for that
18 indication, at that concentration, at the moment.

19 Could I ask, if you don't mind, if Dr.
20 David Birnbach speaks to this issue, because we have
21 been working with David on how best to approach this
22 issue, and I would like to ask if he can just address

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1 it?

2 DR. HORLOCKER: Dr. Birnbach.

3 DR. BIRNBACH: Thanks. I'm David
4 Birnbach. I'm an Associate Professor at the College
5 of Surgeons, Physicians and Surgeons at Columbia
6 University.

7 I am also the President of the Society for
8 Obstetric Anesthesia and Parenecology. More important
9 to this discussion, I am Director of Obstetrics
10 Anesthesiology and St. Luke's Roosevelt Hospital
11 Center in New York City, that has a very large and
12 high risk population of pregnant patients.

13 I have been in discussions with
14 Chiroscience for several years, because as the fourth
15 point there shows, I believe, as do many practicing
16 obstetric anesthesiologists, that we need to do
17 studies, that there is a need for a new epidural agent
18 in obstetrics, and that 0.75% levobupivacaine might be
19 such an agent.

20 I can't say that it is such an agent, no
21 studies have been done; however, I would like to
22 address the fact that if a black box warning is put on

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1 this drug, it would just about invalidate any
2 possibilities of the studies occurring, or of a
3 practice changing for use of that better drug.

4 There are three or four points, I only
5 have a very few number of slides, probably for the
6 first time in my life, and I would like to discuss
7 several issues.

8 First of all, the recent animal studies do
9 not support the decision to put a black box on 0.75%
10 bupivacaine for obstetrics. And they surely don't
11 support putting a black box on obstetrics for 0.75%
12 levobupivacaine.

13 In 1983, the data in those days -- and
14 this was predominantly animal data -- suggested that
15 pregnant patients were far more sensitive to the
16 effects of bupivacaine than nonpregnant patients.

17 This was an American disease. Patients
18 didn't die of 0.75% cardiotoxicity from bupivacaine,
19 in any other country than the United States. And the
20 presumption, especially on the part of anesthesiologists in
21 the U.K., was that it was the practice of anesthesia
22 in the United States, not the drug.

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1 You can kill a patient with any local
2 anesthetic, if you administer it inappropriately. And
3 in obstetrics, inappropriate would be, putting 25 to
4 30 mls through the epidural needle, without a test
5 dose, without waiting and incrementally dividing the
6 dose.

7 Recent animal studies, and Professor
8 Mather showed us this morning, Alan Santos' studies,
9 and this is something that I think we should discuss
10 for a few seconds, the recent studies do not support
11 the differences in cardiotoxicity between pregnant and
12 nonpregnant sheep.

13 That was central to the original black box
14 warning just for obstetric patients. After all,
15 obstetric patients were more sensitive to the effects
16 of local anesthetics. If obstetric patients aren't
17 more sensitive, than perhaps you should be thinking
18 about a warning of 0.75 for everyone, or no warnings.

19 The second point that I would like to make
20 is that levobupivacaine is, we think, less cardiotoxic
21 than bupivacaine. And more importantly, our practice
22 today is dramatically different than our practice was

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1 20 years ago, and it is 20 years ago next month that
2 Albright first came forth with his patients who had
3 cardiotoxicity with 0.75% bupivacaine.

4 So, Alan Santos in 1995, in the first of
5 his new studies, said the systemic toxicity of
6 ropivacaine, this was a ropivacaine study, and now
7 it's been duplicated for levobupivacaine, is not
8 enhanced by ovine pregnancy, but neither is that of
9 bupivacaine.

10 Now, this is about the strongest statement
11 that a researcher. Now, this is about the strongest
12 statement that a researcher can make, because he
13 invalidated his own studies, and those of Dr.
14 Morashima in publishing this. And in so doing, he
15 discussed in the discussion section, that the present
16 state of the art of chief research was not anywhere
17 near where it was 20 years ago.

18 And doing his studies today, with the
19 sophistication that he was capable of, he could not
20 find any difference in cardiotoxicity between pregnant
21 and nonpregnant sheep.

22 Now, if we look at the best database for

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1 maternal deaths, if we are going to assume that
2 mothers are more susceptible to the effects of
3 epidurals, the best would be the U.K., the Continental
4 Inquiries Into Maternal Mortality of England and
5 Wales.

6 And the most recent data we have is the
7 1970 to 1987 data. During that period of time, 139
8 mothers died in the U.K., and of these, only 11
9 received epidurals. And of those, one died of
10 untreated hypotension; five died of total spinal
11 anesthetics after spinal; one died of cardiac disease,
12 she had critical aortic stenosis and was given a one
13 shot bolus drug; one died of complications of PIH,
14 including seizures, and one had an amniotic fluid
15 embolism which was found on autopsy.

16 Not a single death during that entire
17 period of time was due to local anesthetic toxicity,
18 with an epidural, as we are worried about, that
19 somehow the practitioner will give a big bolus, no
20 testing, and it will go intravascularly.

21 Now, I inferred that our practice is not
22 what it was 20 years ago. We now as a rule

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1 incrementally divide our doses. And the current
2 standard of care in the United States, is in
3 obstetrics, not to give bolus drugs.

4 I did a search of every textbook, and
5 every single textbook, both of anesthesiology and
6 obstetric anesthesiology, and that includes five in
7 the United States, all say clearly and
8 incontrovertibly, that a dose must be fractionated in
9 obstetrics.

10 Number two. The switch has occurred
11 several years ago. The vast majority of practitioners
12 are now using multi-orifice catheters. And two recent
13 studies by Norris and colleagues in St. Louis have
14 shown that aspiration of a multi-orifice catheter has
15 a greater than 99.5% chance of reliably detecting
16 intravascular placement just on aspiration. That is
17 nowhere near the case with single orifice catheters.

18 So, 1983, the only catheters available
19 were single orifice catheters. More importantly, we
20 now have standards for regional anesthesia practice in
21 obstetrics, and in the main operating room. Things
22 that we didn't have 20 years ago.

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1 Now, if you look at Albright's cases, and
2 again, there was some question about Albright's
3 publication of these cases, this was an editorial.
4 There was some concern that Albright was jumping the
5 gun, and incriminating a drug rather than the
6 practice.

7 If you look at Albright's cases, all the
8 deaths -- and they were not all due to bupivacaine
9 0.75%, there were some due to epidacaine as well.
10 None of the 11 were resuscitated appropriately.

11 As a matter of fact, in four of them,
12 there was no anesthesiologist present. So, in 1999
13 standard of care, that would not be a problem, because
14 we are present during regional anesthetics. We teach
15 incremental boluses, and we have resuscitative
16 equipment immediately available.

17 Last, there was a decreased use of
18 epidurals for elective Cesarian Sections, and we are
19 using epidurals more and more for a select group of
20 patients, and that would be a high risk group of
21 patients.

22 And that brings me to the last point,

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1 which is why I, as a practicing obstetric
2 anesthesiologist, and representing OB anesthesia as
3 President of SOAP, believe that there is a need for a
4 different epidural agent.

5 The options that we have right now, if you
6 have a severe preeclamptic patient, there are only
7 four options if you want to do it under a slow,
8 controlled, regional anesthetic, which is what all
9 practicing obstetric anesthesiologists want to do.

10 We don't want to give a general
11 anesthetic. These patients have oral-pharyngeal
12 swelling, or difficult intubations, or full stomachs.
13 And so we are left with a choice. There is 2%
14 lidocaine plain, and we tend to use somewhere between
15 20 and 25 ml to get a block for Cesarian Section, and
16 that is a toxic dose of lidocaine in a patient who has
17 a risk factor for seizure.

18 You can lose 2% lidocaine with
19 epinephrine, and it has been reported, a case report
20 three years ago in Regional Anesthesia by Hadzich and
21 colleagues, demonstrated that they were able to double
22 the diastolic blood pressure in a patient who was

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1 already at risk for seizure, by giving an epinephrine-
2 containing solution.

3 The block worked. It was in the epidural
4 space, but there is an intravascular absorption of
5 epinephrine and it is relatively contraindicated in a
6 severe preeclamptic patient. You can use 3%
7 chloroprocaine and the block will come on almost
8 instantly, like a spinal, but we don't the luxury of
9 a slow controlled block.

10 Or, you can use 0.5% bupivacaine, which is
11 more or less what many of us do, and to put it in lay
12 terms, that is a wimp of a drug. 0.5% bupivacaine for
13 Cesarean Section does not give the solid block that
14 many obstetric anesthesiologists are looking for,
15 which has caused many to look for options.

16 And one of the options that three
17 textbooks discuss is the mixture of lidocaine with
18 bupivacaine. No data to support that that makes it
19 any safer than using either of the drugs alone.

20 There are select groups of patients who
21 would benefit from having the ability of the
22 anesthesiologist to use a stronger agent in the

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1 epidural space, that allowed us to have a slow
2 controlled epidural block.

3 Right now we don't have such an agent.
4 I'm not advocating that Chiroscience be given
5 permission to go out and advertise that 0.75%
6 levobupivacaine is safe and effective for Cesarian
7 Sections, especially not in sick patients.

8 What I am advocating is, that we need to
9 do the research. And the only way we are going to do
10 that is to look realistically at why the black box was
11 put there 17 years ago, and whether it needs to be
12 there today.

13 And as a practicing obstetric
14 anesthesiologist, my opinion is that it does not.

15 DR. HORLOCKER: Dr. Watcha.

16 DR. WATCHA: A question for you, sir. Are
17 there such studies underway, planned?

18 DR. BIRNBACH: The planning is underway.
19 The studies are not underway.

20 DR. WATCHA: Okay. This is a committee
21 that has been asked to look at a drug, to approve a
22 drug. If there are patient populations that are not

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1 covered adequately by the current plan, then I think
2 we need to get back the data, because already today,
3 we have got a lot of material where the data is
4 incomplete. Where the data is present with the --
5 without -- the FDA doesn't seem to have any of the
6 data.

7 If we are going to be looking at this
8 aspect of it, we need to come back here with the data.

9 DR. BIRNBACH: We're not, my understanding
10 is that Chiroscience is not applying at this point for
11 the use of 0.75% in obstetrics. And these are studies
12 that can easily occur. They would take several years
13 to carry out. And they can occur, once
14 levobupivacaine is on the market, if it is approved.

15 It does not need to be approved for use in
16 obstetrics. On the other hand, if the black box
17 warning is there, it will contraindicate the use,
18 medical legally, and I believe that your statement is
19 correct, that no practitioner, if that black box is
20 there, would dream in this medical legal climate, even
21 if it was a better drug, of using that drug.

22 It would, more to the fact, preclude the

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1 studies. Because if a black box warning appears, how
2 many patients will allow that drug to be used as part
3 of a study?

4 If there were evidence that
5 levobupivacaine caused cardiotoxicity, if there were
6 evidence that the practice today, like it was 20 years
7 ago, put patients at risk, then it would be different.

8 What I am saying is, that this
9 conversation should be separated from the question
10 about levobupivacaine and whether or not it should be
11 approved.

12 This is the conversation about whether or
13 not the warning needs to preclude its use right now,
14 and I believe that the evidence doesn't support, at
15 this juncture, putting that warning on.

16 DR. HORLOCKER: I think Dr. Birnbach has
17 given compelling evidence why we really don't need the
18 0.75% racemic bupivacaine black box warning, as Dr.
19 Smiley was saying, that really the toxicity is going
20 to occur with a large injection, single injection,
21 probably with a peripheral nerve block, rather than
22 with a continuous catheter technique where we can load

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1 it incrementally.

2 I would like to get back to the actual
3 discussion about racemic bupivacaine, because it will
4 easily facilitate the rest of our discussion,
5 regarding levobupivacaine. What are the concerns,
6 considerations, of the Advisory Committee regarding
7 the removal of the black box warning of racemic
8 bupivacaine? Dr. Parris?

9 DR. PARRIS: I feel, if it were to be
10 removed, in the general population of our lay
11 colleagues, out of academic institutions, that would
12 give the impression that it is safe, or it is
13 certainly not very cardiotoxic.

14 I think Dr. -- the last speaker, made a
15 very persuasive argument for not having the black box
16 attached to the levobupivacaine package insert, but
17 I'm a little uncomfortable, because what happens if
18 you do have a -- for example, you're doing a Biers
19 Block, and when you release the tourniquet, you're
20 putting a large amount of local anesthetic into the
21 circulation.

22 Of course, if you do good practice, you

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1 should reinflate the cuff to prevent that, but what
2 happens if the cuff fails? What happens if you are
3 doing an intercostal nerve block where the levels, the
4 blood levels are highest? What happens in those
5 situations?

6 DR. HORLOCKER: But again, I would like to
7 remind you, the black box warning pertains to 0.75%
8 bupivacaine in obstetrical use, so that's why it
9 really is -- it's related to a small subset of
10 patients, and it has nothing to do with a Biers Block,
11 or a single dose injection.

12 DR. PARRIS: But my point is that --

13 DR. SMILEY: That was precisely my point.

14 DR. PARRIS: That's the point. That's the
15 --

16 DR. SMILEY: That was mine.

17 DR. PARRIS: -- practice was the same. I
18 mean, in those days, 20 years ago, there as more
19 tendency to give a large bolus, and that is analogous
20 to releasing the local anesthetic after a Biers Block,
21 or through an intravascular injection.

22 DR. SMILEY: That was precisely my point,

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1 is that, I believe that the black -- no one reads
2 them, anymore. I mean, this drug has been --
3 bupivacaine has been around for a long time, nobody
4 reads that black box anymore.

5 In fact, if they did, it would be
6 counterproductive, because the implication is that the
7 problem with bupivacaine is that pregnant women have
8 cardiac arrests, if you do it wrong.

9 That's not the problem. The problem is,
10 if you give too much of it, and you get a blood level
11 real fast, however you manage to do that, with a Biers
12 Block, with an interscabian block that goes into the
13 jugular vein or carotid artery, with an epidural
14 catheter or a needle that's in vessel, you may kill
15 somebody.

16 And yes, you may kill them easier with
17 bupivacaine than with lidocaine, and it may be more
18 difficult to resuscitate, and pregnant women are more
19 difficult to resuscitate, no matter why they arrest.
20 But that's a different issue from any particular
21 drugs.

22 So, my point is that, that's -- if you

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1 need the black box, and I don't think you do. I think
2 you need anesthesiologists trained in anesthesiology,
3 but if you needed a black box, that wouldn't be the
4 black box warning.

5 The black box warning would be, don't give
6 it intravascularly. I mean, I've had a little more
7 time to write it, but it wouldn't be, don't use this
8 drug, this concentration.

9 It wouldn't focus on concentration,
10 because it's dosed, also. We know that also. It's
11 not 0.75%, it's how many milligrams are in the blood,
12 how many nanograms/ml are at the concentration?

13 I know most of you know this, but I think
14 it's important that -- I mean, you're making a very
15 good point, that you know, if you do a Biers Block
16 with this drug, and think it's not toxic, because it
17 doesn't have a black box, and give a ton of drug and
18 then take the tourniquet off a few minutes early, or
19 an hour early, yes, you may have a problem, but that's
20 not what the black box says, anyway.

21 So, it should just be, you know, you don't
22 know how to use local anesthetics.

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1 DR. PARRIS: Another, just a follow-up to
2 this. Local anesthetics today are not only used by
3 trained anesthesiologists. In the realistic work of
4 pain medicine, there are neurologists; there are
5 radiologists doing nerve blocks.

6 And they don't have the same sophisticated
7 knowledge of the pharmacokinetic properties of the
8 drugs as anesthesiologists are supposed to have. They
9 just look at the package insert, and that's their
10 basis.

11 DR. HORLOCKER: But again, that black box
12 wouldn't assist them with that decision-making
13 process, since it only is applying to the obstetrical
14 population. Dr. Reves?

15 DR. REVES: I actually had written, even
16 though it's not perfect English, what I was thinking,
17 as you said you hadn't written it, and mine would be
18 a warning that says, animal studies demonstrate CNS
19 and cardiac toxicity that is dose-related, thus equal
20 volumes of higher concentration will be more likely to
21 produce toxicity. Something along those lines.

22 I would remove the black box for both

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1 drugs.

2 DR. HORLOCKER: Okay. Dr. Carlisle?

3 DR. CARLISLE: I'm still a little
4 concerned about the whole issue of resuscitation, and
5 I actually disagree with our last discussant, in that,
6 he implied that, had there been adequate efforts at
7 resuscitation, with the bupivacaine episodes, that
8 these patients would all have been resuscitated.

9 And I'm not sure that we actually have
10 evidence that that is true. In fact, we have, we are
11 working under the assumption that these patients have
12 a very difficult to resuscitate rhythm, and we have
13 seen no evidence that that's not true, today, with
14 either of these drugs.

15 DR. HORLOCKER: Dr. Ashburn?

16 DR. ASHBURN: She beat me to the punch.
17 I think, because I think that, as Dr. Reves was
18 saying, one of the important issues is that a drug of
19 higher concentration given in equal volumes is going
20 to lead to higher, or the potential for higher
21 systemic doses, but the other issue is, is that there
22 is some evidence, at least the presumption, that

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1 individuals who do have a malignant arrhythmia with
2 bupivacaine are harder to resuscitate.

3 And that seems to be, if you are going to
4 black box, those are the issues, or those are the
5 warnings, however it is communicated, and I must say,
6 I'm not so sure that I've seen data, other than animal
7 data, that show that levobupivacaine is any different.
8 And we certainly have seen no data with regard to the
9 ability to resuscitate, once a critical event has
10 occurred.

11 And with regard to the last talk, there
12 were a couple of contraindications that actually
13 brought -- at least a statement that was made on the
14 first slide that said, local anesthetic toxicity
15 studies in animals do not necessarily predict what
16 will happen in humans.

17 That was one of the bullets on the first
18 slide, which of course, if you believe that, then all
19 the data on cardiac toxicity that was presented by the
20 Sponsor, would be immediately suspect, with regard to
21 the cardiac safety claims of this product, compared to
22 the other.

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1 So, I don't know which argument the
2 Sponsor would like us to believe, because those
3 bullets seem at least to me to be in a bit of
4 contradiction.

5 DR. HORLOCKER: Dr. Watcha.

6 DR. WATCHA: A question for the FDA. You
7 get reports of toxicity of various drugs, again, data
8 incomplete and not everything that is reported.

9 Since that black box was put in, have we
10 had additional reports of 0.75% bupivacaine toxicity
11 for non-obstetric patients?

12 DR. MCCORMICK: That's a good question.
13 I thought you were going to ask about obstetric
14 patients, and I was going to make the point that we
15 are not seeing that anymore.

16 We'll have to go back and look at that.
17 We don't have that information, offhand, but that's a
18 good question.

19 DR. WATCHA: And the second question
20 correspondingly is, you may not put in a black box
21 warning, but we could certainly put in something along
22 the lines of which the other folks have mentioned, so

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1 that we do have a warning, but not something that will
2 prevent investigation of this drug for the full
3 obstetric anesthesia, and that to me would seem to
4 balance what we as a Committee need to do, is to
5 balance the risks and benefits of this.

6 DR. HORLOCKER: Dr. Tobin?

7 DR. TOBIN: Teresa, if I can read from the
8 large binder that you sent to us in the materials.
9 This is the transcript from many years ago, and
10 there's a relation regarding, what is the black box
11 for, and let me quote from this. This is page 257.

12 "Special problems, particularly those that
13 may lead to death or serious injury may be required by
14 the Food and Drug Administration to be placed in a
15 prominently displayed black box.

16 "The boxed warning ordinarily shall be
17 based on clinical data, but serious animal toxicity
18 may also be the basis of a boxed warning, in the
19 absence of clinical data."

'20 Well, considering the toxicity of all the
21 drugs that we use, everything could wind up in a black
22 box. I'm certainly, again, in agreement with my

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1 colleagues that there is a need for a prominent
2 warning here.

3 But I caution us not to forget the lesson
4 of history here, that if we have had a diminution in
5 the reports of toxicity from 0.75%, I cannot be
6 confident that that is because of the change in
7 anesthetic practice versus the diminished use of that
8 drug.

9 So, I think we have to be very cautious
10 about saying, it's safe and we can go ahead and
11 eliminate the black box. I'm certainly willing to
12 accommodate and go towards a strong warning that
13 doesn't necessitate the black box, but maybe bold
14 print.

15 And I liked some of what Dr. Reves had
16 said earlier, something along those lines, but I think
17 we can't just assume that by history, the change in
18 practice is the reason that we have seen decreased
19 morbidity and mortality.

20 DR. HORLOCKER: Dr. DiMarco, could you
21 summarize the cardiac toxicity data between the two
22 drugs as you have done your evaluations?

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1 DR. DiMARCO: Yes, I think actually, as a
2 cardiac electrophysiologist, all the drugs I use does
3 have a black box, because they're all pro-arrhythmic,
4 and that's -- you start off with that approach.

5 I was asked specifically to compare a few
6 things, and I'll start with the preamble that I think
7 the Sponsor had a very difficult job, because what
8 they are trying to do is in an ethical situation with
9 nondangerous doses and normal volunteers are in
10 clinical use, look at a very rare event that usually
11 occurs with what would be a massive dose, overdose, or
12 a poisoning due to an inadvertent injection or too
13 rapid absorption.

14 However, when I looked at those things,
15 let's look at the normal volunteer studies, what the
16 Sponsor calls contractility changes, I was a little
17 unconvinced by those for, one, I couldn't tell whether
18 they were related to CNS effects on the heart.

19 There are changes in heart rate, there are
20 changes in blood pressure. Even the changes that are
21 seen are relatively small and the differences between
22 the drugs are quite minor. So, I wasn't impressed

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1 that there was hard evidence that there were changes
2 in contractile function at that period of time.

3 The electrocardiographic changes are
4 interesting that they look at, and I think that I'm
5 particularly worried by Dr. Woosley's statement
6 earlier today, where he said where he reanalyzed them
7 and found even the changes that are reported here,
8 weren't present because of a different method of
9 analyzing the QT interval.

10 And that's, I didn't have that information
11 when I did the report, but even so, the changes that
12 are seen, really didn't achieve statistical
13 significance. They're very small.

14 Some of the things that are of interest
15 are for example, there is one study that shows a
16 change in the PR interval, but if you look at the
17 Sponsor's slide where he is looking at his meta-
18 analysis of the ECG review, the two studies that use
19 the highest doses didn't show a change in the PR
20 interval, so you would think that that would be the
21 place where you would see the most effect.

22 So, I really wasn't convinced that in the

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1 studies that were shown to me, there were major
2 changes in the cardiovascular profile of the drugs,
3 because there really weren't, you couldn't demonstrate
4 them at these doses, even if they were there.

5 The final thing I will say, and I didn't
6 say this in my report is that, you know, in looking at
7 these compounds, the toxicity that you are seeing, and
8 that's been described in the literature, really looks
9 to me like a Class 1 antiarrhythmic drug overdose.

10 That's where we get non-resuscitateable
11 arrhythmias. That's where you get reflex
12 tachycardias, which because of use-dependence make the
13 arrhythmias -- make the electrophysiologic effects
14 more pronounced. You can't defibrillate because you
15 have got changes in defibrillation threshold, and you
16 have adverse hemodynamic effects.

17 And so, I'm not sure that the QT interval
18 --

19 DR. SMILEY: Do you have any suggestions
20 about what to do about it when it happens?

21 DR. DiMARCO: Well, you know, everything's
22 -- we don't resuscitate them well, either. You know,

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1 people have tried things, but the literature, really,
2 there are a few positive reports with hypertonic
3 saline. There is some negative reports. So I'm not
4 sure, in the resuscitation studies which are using
5 Bretyllium, which is something that you might think is
6 an ischemically-mediated re-polarization phenomena,
7 may be in a different direction.

8 And I think the final statement that Dr.
9 Mather had, that when he gives it directly to the
10 heart, he doesn't show a change, suggests to me that
11 at least something other than just differences of the
12 two drugs specifically on the heart have to be
13 operational.

14 DR. HORLOCKER: Dr. Rohde. Comments on
15 black box warnings on either or both levobupivacaine
16 and bupivacaine.

17 DR. ROHDE: My feeling is that they are
18 not needed.

19 DR. HORLOCKER: Ms. Connolly?

20 MS. CONNOLLY: I would say I would be in
21 agreement with --

22 DR. HORLOCKER: Use the microphone,

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1 the lines of what people I think are saying is, that
2 I don't think we need a black box, specific black box
3 warning anymore, but there should be a modified
4 warning about dose adjustments and total dosage
5 advice, rather than the black box thing, which I think
6 is -- you know, it's overly-dramatic and overly-
7 simplified, and based upon too many -- too little
8 information.

9 DR. HORLOCKER: Dr. McCormick, would you
10 like us to take a formal vote for the removal of the
11 black box warning of bupivacaine? Would that be
12 helpful to you all now?

13 DR. MCCORMICK: Yes, it would. Actually,
14 if I may make a point of protocol. I believe we had
15 a period of public comment --

16 DR. HORLOCKER: Oh, I'm sorry.

17 MS. CONNOLLY: Perhaps before we have the
18 vote, we should invite members of the public to --

19 **Open Public Hearing**

20 DR. HORLOCKER: Yes. Thank you very much.
21 We did just jump right past the open public hearing,
22 because I earlier had assumed there would be no other

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1 -- is there anyone from the audience that would like
2 to speak? I apologize for the breach in protocol.
3 Thank you.

4 **Committee Vote**

5 DR. HORLOCKER: All right, at this time
6 then let's take a formal vote among Committee members
7 on the removal of the black box warning of
8 bupivacaine, and the placement or actually it's for
9 the removal of the black box warning on
10 levobupivacaine, also, so which, if either of these
11 drugs, would you want a black box warning on? Dr.
12 Reves?

13 DR. REVES: I wasn't raising my hand to
14 speak.

15 DR. HORLOCKER: No, we're going to go
16 around and vote. It doesn't matter whether you raised
17 your hand or not.

18 DR. REVES: I think we probably should do
19 them separately, but I would say --

20 DR. HORLOCKER: Okay, we could do them
21 separately.

22 DR. REVES: But I'm for not putting one on

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1 levo, and taking off the one on bupivacaine.

2 DR. PARRIS: Before we vote, Madam
3 Chairman, are you, in removing the black box from
4 bupivacaine, and not putting it on levobupivacaine,
5 are you at the same time suggesting that we have
6 language in the package insert, recommending that --

7 DR. HORLOCKER: It would probably be very
8 similar to that with ropivacaine that has a strong
9 warning in capital letters. This would be up to the
10 FDA to formally develop the labor.

11 But, correct. There would be not a lack
12 of warning or a lack of use of common sense with dose
13 and concentration.

14 DR. PARRIS: Okay.

15 DR. MCCORMICK: May I just make a point?

16 DR. HORLOCKER: Yes, Dr. McCormick.

17 DR. MCCORMICK: An that is that, before we
18 do take any action on the bupivacaine label, which we
19 haven't gotten really specifically recently studied,
20 we would certainly want to go back and look at all of
21 the adverse events that have been reported to us.

22 DR. HORLOCKER: Okay. Would you still

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1 prefer to have us at least make our --

2 DR. MCCORMICK: I think it would be useful
3 to hear your opinions. Definitely.

4 DR. HORLOCKER: Okay. Dr. Smiley?

5 DR. SMILEY: Yes. I would remove that
6 black box warning from both drugs.

7 DR. HORLOCKER: Okay. Dr. Carlisle?

8 DR. CARLISLE: I would remove the black
9 box warning and replace it with strong language in
10 incremental dosing.

11 DR. HORLOCKER: Both drugs?

12 DR. CARLISLE: Both drugs.

13 DR. HORLOCKER: Okay. Dr. Ashburn?

14 DR. ASHBURN: I agree.

15 DR. HORLOCKER: Okay. Dr. Watcha?

16 DR. WATCHA: As above. Agree. For both.

17 DR. HORLOCKER: Dr. Tobin?

18 DR. TOBIN: I agree for both.

19 DR. HORLOCKER: Dr. Rohde?

20 DR. ROHDE: Yes.

21 DR. HORLOCKER: Removal for both, or?

22 DR. ROHDE: Well, one doesn't have it,

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1 right?

2 DR. HORLOCKER: Okay. It's inferred,
3 unless we take it off. Ms. Connolly?

4 MS. CONNOLLY: And I again, that which
5 currently exists.

6 DR. HORLOCKER: Use the microphone,
7 please?

8 MS. CONNOLLY: That which currently
9 exists, I agree to be removed.

10 DR. HORLOCKER: Okay. Dr. Savarese?

11 DR. SAVARESE: Again, one more point of
12 information to make sure I understand, I mean I'm sure
13 I do, but we're talking about a more ropivacaine-like
14 label, correct?

15 DR. HORLOCKER: Right. For lack of a
16 better analogy, but, yes.

17 DR. SAVARESE: Okay, I agree with that,
18 and I also favor the no black box for either of the
19 two.

20 DR. HORLOCKER: Dr. Parris?

21 DR. PARRIS: The two.

22 DR. HORLOCKER: I vote for removal for

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1 both. Okay, let the minutes note that it was a
2 unanimous vote.

3 (Whereupon, the Committee having been
4 polled on the previously-noted proposal, returned a
5 unanimous vote.)

6 Let's move on to Question No. 1, because
7 this one also does have some significant labeling
8 inferences. Even though both drugs may end up without
9 black box labeling, there still is the possibility
10 that there could be an advantage to using
11 levobupivacaine because of a potential decreased
12 cardiac toxicity. So, we really still need to address
13 this issue.

14 "Has the Sponsor adequately evaluated
15 levobupivacaine's potential for cardiac toxicity at
16 the labeled dose? If not, what further studies are
17 needed?"

18 Dr. Reves, would you like to make your
19 comments?

20 DR. REVES: Well, I think we discussed the
21 difficulties in doing a sort of dose finding study on
22 toxicity in humans.

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1 The animal data are persuasive that there
2 seems, that there certainly is dose-related toxicity,
3 and moderately persuasive that there's a difference
4 between these two drugs, that begs the question of
5 whether there is equal -- if they are equipotent.

6 But I think we'll never get the perfect
7 human toxicity study, so I think they've done as much
8 as is reasonable to learn about this.

9 They are at the flat end of the curve, but
10 that's where they have to be by the IRBs.

11 DR. HORLOCKER: And just as a reminder,
12 the previous Advisory Committee had requested that the
13 Sponsor document at least a 25% increase in safety
14 over bupivacaine in a clinical study, is the way that
15 they had previously set the goals for the statement to
16 be able to support an increase in safety.

17 DR. REVES: I think they showed it in the
18 animals and not in the humans.

19 DR. HORLOCKER: Dr. Smiley?

20 DR. SMILEY: I agree completely. I think
21 we are, I suspect we're in tremendous consensus on the
22 human studies being difficult and unpersuasive, and

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1 that the animal studies are moderately persuasive.

2 DR. HORLOCKER: Dr. Carlisle?

3 DR. CARLISLE: I'm still troubled by the
4 lack of the resuscitation data, but in terms of CNS
5 toxicity, I agree that I think the animal data is
6 moderately, are moderately persuasive.

7 DR. HORLOCKER: Certainly, one of the
8 options that this Advisory Committee has is to wait
9 until the resuscitation data are available, before we
10 make our final assessment of this.

11 We can consider that in our vote, also,
12 when we come around again, because those data are
13 critical, but perhaps enough data already exists to
14 still make the statement. Dr. Ashburn?

15 DR. ASHBURN: I think, based on the
16 question, the way this question is worded with regard
17 to -- I guess it depends on what you are looking for.

18 If it's just cardiac toxicity with regard
19 to this particular local anesthetic agent, I think,
20 yes, the studies are sufficient.

21 Is it sufficient to claim superiority over
22 bupivacaine, that I'm less sure of. And even

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1 understanding the difficulty in human trials versus
2 animal trials, that at least in my mind is a little
3 more problematic.

4 And I think that even when the current
5 study is done with regard to resuscitation, it seems
6 to me that an n of 6 in each study group with regard
7 to resuscitation is insufficient to have enough
8 statistical power to be able to identify whether or
9 not the animals, there is any difference in the study
10 drug.

11 So, even though the statistical analysis
12 has been completed, I would say that I think an n of
13 6 is insufficient to be able to really go home on
14 animal studies, whether or not these drugs are going
15 to be different when that study is done.

16 DR. HORLOCKER: We could of course request
17 additional studies and if I remember correctly from
18 the ropivacaine discussions, there is a different
19 resuscitateability, depending on which animal model is
20 selected.

21 And so, using an alternate model might
22 also give us additional data, and so there is that

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1 possibility.

2 DR. ASHBURN: I concur.

3 DR. HORLOCKER: Dr. Watcha.

4 DR. WATCHA: One of my concerns, Madame
5 Chairman, has been the fact that we really do not even
6 know which of the groups those patients -- those
7 animals were.

8 We try to make decisions on incomplete
9 data, inadequately presented and summarized data, and
10 if we need to have another meeting to come back and
11 see all the data properly, whether we have a chance to
12 review the data before the meeting, that would be
13 fine, too. We are making decisions on data that is
14 incomplete and inadequate at present.

15 And again, with regard as mentioned
16 before, with regard to certain patient populations, we
17 have no data on it.

18 DR. HORLOCKER: Excellent points. Dr.
19 Tobin?

20 DR. TOBIN: I think the Sponsor has
21 provided sufficient data in the animal studies to
22 indicate that levobupivacaine is at least as safe as

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1 the current racemic mixture.

2 However, I think there is insufficient
3 data, once again, pointing to the resuscitation
4 studies, to demonstrate superiority of whether or not
5 the morbid events do occur, and whether or not
6 resuscitateability is indeed better in the
7 levobupivacaine group. And I strongly encourage them
8 to go back and increase the size and power of those
9 studies.

10 Secondly, I would like to echo what Dr.
11 Watcha has said, which is that we do not know the
12 potential age-related toxicity of this drug, and we
13 know of some toxicity with bupivacaine in the young
14 human patients.

15 And I would like to encourage them to
16 consider a developmental model, as it is clear that
17 bupivacaine is in widespread use in the pediatric
18 population, including the newborn.

19 In the Sponsor's or in the FDA's prepared
20 proposed package insert, there is incomplete reference
21 to pediatric indications, and I would like to be sure
22 that even the data that we are presented today are

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1 recognized that they only included infants greater
2 than age six months, and that the potential indication
3 of ages zero to 18, it is not appropriate.

4 DR. HORLOCKER: I also concur that the
5 lack of resuscitation data is worrisome, and if I were
6 the Sponsor, I would actually want to get that data
7 out so that you could claim a true superiority, if one
8 exists, over bupivacaine.

9 I would hope that if the data, if this
10 drug is released without that data, that the label
11 would actually reflect that and say that, while there
12 may be decreased cardiac toxicity, the
13 resuscitateability between this drug and bupivacaine
14 is unknown at this point in time, because I think we
15 really have to do, as others have mentioned, state the
16 facts as they exist today, and as someone has earlier
17 said, what we don't say is as important as what we do
18 say.

19 And so, we have to stress what we know and
20 what we don't know, and the label could always be
21 amended as that data come in, or the drug could be
22 held until we get those data. And it could be

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1 included at that point in time. Dr. Rohde?

2 DR. ROHDE: One thing seems to me to be
3 perfectly clear, we could search forever and never
4 exhaust all the possible subgroups where we might find
5 one drug being superior to the other.

6 So, it seems to me, and that's not really
7 the issue. The real issue is what the Sponsor has
8 presented, which is pretty convincing, except for the
9 resuscitation data.

10 I would like to see for something like
11 this a good follow-up by FDA in terms of drug
12 surveillance, because that's the only way that you'll
13 get data on all these possible subjects, particularly
14 the ones that are going to be very, very small.

15 It might take ten years before data will
16 come in on these groups, and if it does, and it's not
17 a drug for that subgroup, that's fine, but that should
18 not penalize the rest of the population for whom this
19 might be very beneficial.

20 DR. HORLOCKER: Ms. Connolly.

21 MS. CONNOLLY: As the consumer
22 representative, I definitely think that the animal

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1 models did show a trend toward CNS toxicity and
2 cardiac toxicity at the labeled doses.

3 However, I do have a concern that the
4 human volunteer studies did not adequately show gender
5 differences. One study was all male, and the other
6 studies said 22 healthy volunteers, but did not break
7 it down according to gender.

8 I am also concerned, too, that we need
9 more studies with regard to the pediatric population.
10 And the lack of resuscitation follow-up study.

11 DR. HORLOCKER: Dr. Savarese.

12 MS. REEDY: Are you saying that the
13 potential for cardiac toxicity is adequately --

14 MS. CONNOLLY: Has been adequately
15 addressed. Yes.

16 DR. HORLOCKER: Dr. Savarese?

17 DR. SAVARESE: Well, I guess my first
18 point is, remember that again, we're doing all of
19 these toxicity comparisons under the assumption that
20 the anesthetic potency is the same.

21 And my question is, do we have enough data
22 to make that assumption, or to make that conclusion?

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1 As far as I know, there have been only a couple of
2 comparative studies of potency in humans, I'm talking
3 about humans.

4 My feeling is that there should at least
5 be one or two more simple comparative studies; you
6 know, simple nerve block comparisons of the two drugs
7 to establish that they are equipotent, beyond any
8 shadow of a doubt.

9 And then with that data in hand, then all
10 I would need is the improved IV toxicity data with
11 respect to resuscitation. I think we're all waiting
12 for that.

13 And the only other possible thing that
14 might be needed is a little bit more IV toxicity data
15 in humans. The sort of study that Walter Nimmo
16 presented. But that's a small number of subjects, and
17 well, I don't know how much more of a chance you want
18 to take in injecting more drug into people, but maybe
19 just pushing it a little bit further, beyond where you
20 did.

21 I'm not saying I would insist on this.
22 This is just what I'm suggesting.

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1 DR. HORLOCKER: In summary, then, would
2 you actually vote to withhold approval of the drug
3 until those studies are done, or would you just make
4 strong recommendations for the Sponsor to perform
5 these evaluations in the future?

6 DR. SAVARESE: Oh, I think, yes. I think
7 they could be done as post-approval. Yes, I don't say
8 we should hold up approval at this point, no.

9 DR. HORLOCKER: Dr. Parris?

10 DR. PARRIS: Following up on this, some of
11 the indirect cardiotoxicity studies have not been
12 reflected in the Sponsor's presentation.

13 For example, drug interactions. There are
14 some drugs that interact with others and thus render
15 them more cardiotoxic than when administered alone.

16 In the presence of hepatic dysfunction,
17 the metabolism may be altered, thus elevated in the
18 blood levels, and making a tendency for more
19 cardiotoxicity.

20 I am not suggesting that we should hold
21 up, but I think these ongoing studies should be
22 reflected, either by surveillance of the FDA, or by

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1 more -- And they may be already there, but it should
2 be presented.

3 I think Ms. Connolly addressed the issue
4 of a sexual, I think an ethnic distribution. For
5 example, what is the effect on African-Americans with
6 sickle cell disease? Or there may be -- you know, so
7 I think that should be represented.

8 And one final comment. About ten years
9 ago, I did some work on bupivacaine-induced muscle
10 atrophy. And I had difficulty getting that study
11 published in the United States. I did a sabbatical in
12 Holland, and I came across 13 cases of muscle atrophy,
13 and that's why the Europeans don't like bupivacaine.

14 And there may be a relationship between
15 muscle atrophy and cardiac toxicity. I don't know.
16 So, maybe we should look at muscle atrophy in
17 patients, following peripheral nerve blocks.

18 And one final comment, I think the last
19 discussant alluded to a British study that was
20 performed between 1970 and 1987, suggesting that there
21 were very few reports of local anesthetic toxicity.

22 I have a little experience in the British

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1 system. Between that period, there was not much local
2 anesthetics administered via epidural. It was
3 primarily by a spinal, because of the Woosley and Rowe
4 disaster of 1954. So that would not be a fair
5 statement to make, to make the inference that there
6 was diminished level of local anesthetic toxicity.

7 DR. HORLOCKER: Dr. McCormick, are there
8 any clarifications that you would like the Advisory
9 Committee to make at this time, or do you have further
10 questions?

11 DR. JEAN: Lucy Jean, FDA. I would like
12 to ask Dr. Savarese about his recommendation
13 concerning the potency. In animals, there are two
14 valid in vivo rat studies testing the efficacy, as far
15 as I know, and then there is an in vitro frog sciatic
16 nerve preparation.

17 In your recommendation, are you referring
18 to animal or human studies, that you would like to see
19 as a Phase 4?

20 DR. SAVARESE: Human, not animal.

21 DR. JEAN: Thank you.

22 DR. HORLOCKER: All right. Are there any

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1 other questions or comments? Yes, sir?

2 DR. GENNERY: If I wonder if I can address
3 one or two of the concerns that are being raised, and
4 just perhaps give a picture as to how some of these
5 things are being addressed?

6 First of all, with regards to pediatrics.
7 We have actually set up and are underway the studies
8 that we agreed to two years ago. Recruitment in some
9 of them has been a bit more difficult, a bit slower
10 than we had perhaps hoped, but two of those studies
11 are now complete.

12 The others are ongoing and as of today,
13 something over 150 children ranging from the ages of
14 two weeks up to 12 years have had levobupivacaine
15 administered by peripheral block, by caudal injection.

16 DR. WATCHA: Unfortunately, in the
17 material that was given to us we have statements that
18 they were incomplete, that the data is not complete,
19 and we are trying to make some decisions, where we're
20 getting statements, written statements as part of our
21 read-out, that says that we don't have that data yet.

22 DR. GENNERY: All I'm trying to do is to

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1 provide you with reassurance that we committed to the
2 program, and we are doing the program.

3 DR. WATCHA: Okay.

4 DR. GENNERY: Secondly, with regards to
5 hepatic dysfunction, we have set up and we are running
6 a study in patients who are having substantial partial
7 hepatectomy for secondary tumors. And we are giving
8 them -- their epidural anesthesia is with
9 levobupivacaine, and their postoperative pain
10 management is with levobupivacaine and Fentanyl.

11 Now, this is a very complex protocol.
12 We're looking at long-term kinetics, and metabolic
13 changes over that period of time, up to about five
14 days postoperatively. It's going to take a long time
15 to do this protocol, but it is underway, and we hope
16 it will provide very high quality science at the end
17 of the day.

18 I think those are perhaps the two
19 outstanding issues. If there are any others, I would
20 obviously be happy to try and address them.

21 DR. HORLOCKER: Are there any other
22 questions?

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1 I just have one statement for the Advisory
2 Committee members then, you don't have to bring all of
3 these books back. Kathleen will send them to your
4 address that they have on file, so that you can leave
5 them at your seat and the FDA will take care of it.

6 I'd like to thank the Sponsors --

7 DR. MCCORMICK: May I have --

8 DR. HORLOCKER: Oh, I'm sorry.

9 DR. MCCORMICK: Excuse me, may I -- I just
10 have one point to make. First to fall, I would like to
11 thank the Committee for a very informative and very
12 helpful discussion today. I think we have
13 clarification of where we need to go with this at this
14 point.

15 I would like to ask a question of the
16 Sponsor, and that is, if you could clarify for us
17 where these resuscitation studies do stand, and
18 whether we can expect them as a Phase 4 commitment?

19 DR. GENNERY: With regard to the dog
20 study, the experimental phase is done and that very
21 preliminary data was presented this morning.

22 The current status is that we are

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1 analyzing the plasma concentration data. That is
2 being carried out at the moment. We are working very
3 closely with Dr. Feldman to get that study completed,
4 fully analyzed, and fully written up, as a final
5 report to file with the Agency, just as soon as we
6 can.

7 DR. MCCORMICK: And with regard to
8 pediatrics, do you have plans for exposure down to the
9 newborn?

10 DR. GENNERY: We hope to be able to
11 present the next pediatric clinical trial report to
12 you within the next few weeks.

13 DR. MCCORMICK: Thank you.

14 MS. REEDY: I am going to give you a
15 little exercise. First of all, thank you very much
16 for coming. I hope you enjoy our meeting room. And
17 this is an excellent Committee, I've really enjoyed
18 working with you. I'll pass that on to Karen.

19 Any of the background materials you would
20 like to take with you, you are welcome to do so. If
21 you would like them shipped to you, put them on the
22 table with your name plate on top of them. If you

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1 would like us to shred them, put them on your chair,
2 please, and we'd be glad to do that, too.

3 DR. WATCHA: If you want some of them, and
4 if you want the others shredded --

5 DR. HORLOCKER: Dr. Tobin, did you have
6 one more comment?

7 DR. TOBIN: Yes, Terese, to the Sponsor.
8 Could I encourage you to at least examine the
9 possibility of doing a toxicity resuscitateability
10 study in a newborn animal model?

11 It comes to mind, the neonatal piglet or
12 the beagle, because I think in the circumstance, we as
13 the pediatric affiliates here, must applaud the FDA
14 for insisting upon pediatric examination of a drug
15 before it comes to market, since children have always
16 been orphan consumers.

17 But, without exaggeration, I will tell you
18 that it is an extremely common practice in academic
19 medical centers to use continuous infusion
20 bupivacaine.

21 This has resulted in significant toxicity,
22 which is now multiply reported in the journals. I

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1 would like nothing better than to have a better drug
2 to use in these small children, to give them
3 perioperative pain and stress relief, as I think it is
4 actually beginning to show improvement in survival
5 with certain diagnoses.

6 DR. HORLOCKER: Okay. Dr. Tobin, did you
7 have a specific model in mind?

8 DR. TOBIN: Either the neonatal piglet,
9 which is used in cardiopulmonary resuscitation work,
10 or in the newborn beagle.

11 **Adjourn**

12 DR. HORLOCKER: I would like to thank the
13 Sponsor, the members of the FDA Panel, and my Advisory
14 Committee members. You have all done an excellent
15 job. Thank you. This meeting is adjourned.

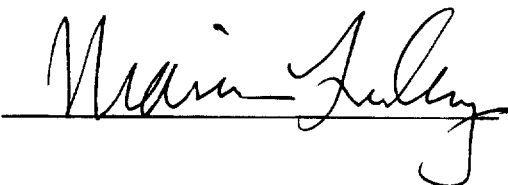
16 (Whereupon, at 3:05 p.m., the 87th
17 meeting of the Anesthetic and Life
18 Support Drugs Advisory Committee was
19 adjourned.)

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CERTIFICATE

This is to certify that the foregoing transcript in
the matter of: 87th Meeting of the Anesthetic &
 Life Support Advisory Committee
Before: DHHS/FDA/CDER
Date: January 12, 1999
Place: Rockville, Maryland
represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
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