FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG ABUSE ADVISORY COMMITTEE

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ALSO PRESENT:

WARREN A. KATZ, M.D.

C O N T E N T S

The Scientific Evidence for Initiating
a Scheduling Action for
Ultram (tramadol hydrochloride)
R.W. Johnson Pharmaceutical Research Institute,
under the Controlled Substances Act

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1 P R O C E E D I N G S

2 (8:33 a.m.)

3 DR. STRAIN: We're waiting for a couple more

4 committee members, but why don't we go ahead and get

5 started?

6 I'd like to call this meeting to order. My

7 name is Eric Strain. I'm the Chairman of the DAAC.

8 I'd like to ask Dr. Templeton-Somers -- well,

9 first, let's go around and introduce the committee and the

10 various members of the FDA sitting at the lead table. Dr.

11 McNicholas, would you please start?

12 DR. McNICHOLAS: Laura McNicholas, the

13 Philadelphia VA and the University of Pennsylvania.

14 DR. SIMPSON: Pippa Simpson, Arkansas

15 Children's Hospital.

16 MS. YAROMA: Dolores Yaroma, Second Genesis,

17 drug and alcohol treatment.

18 DR. KHURI: Elizabeth Khuri, Cornell Medical

19 Center and Rockefeller University.

20 DR. ANDORN: Anne Andorn, St. Louis University

21 in St. Louis, Missouri, and the St. Louis VA.

22 DR. WEINTRAUB: Mike Weintraub, the Director of

23 ODE V.

24 DR. McCORMICK: Cynthia McCormick, Director,

25 Division of Anesthetics, Critical Care, and Addiction

1 Products, FDA.

2 DR. KLEIN: Michael Klein, Team Leader,

3 Controlled Substances.

4 DR. BRASE: David Brase, pharmacologist with

5 the FDA.

6 DR. FRANK: Blanche Frank, New York State

7 Office of Alcoholism and Substance Abuse Services.

8 DR. LLOYD: Llyn Lloyd, Arizona State Board of

9 Pharmacy.

10 DR. de WIT: I'm Harriet deWit from the

11 Department of Psychiatry at the University of Chicago.

12 DR. TEMPLETON-SOMERS: Karen Templeton-Somers,

13 Executive Secretary to the DAAC, FDA.

14 DR. STRAIN: I'm Eric Strain from Johns Hopkins

15 University.

16 DR. YOUNG: Alice Young, Wayne State.

17 DR. MEYER: Roger Meyer, consultant, and

18 Georgetown University.

19 DR. STRAIN: And I think that's everybody,

20 okay.

21 Dr. Templeton-Somers, would you go over the

22 conflict of interest statement please?

23 DR. TEMPLETON-SOMERS: The following

24 announcement addresses the issue of conflict of interest

25 with regard to this meeting and is made a part of the

1 record to preclude even the appearance of such at this
2 meeting.
3 Based on the submitted agenda for the meeting
4 and all financial interests reported by the participants,
5 it has been determined that all interests in firms
6 regulated by the Center for Drug Evaluation and Research
7 which have been reported by the participants present no
8 potential for a conflict of interest at this meeting with
9 the following exception.
10 In accordance with section 208(b)(3), Dr. Roger
11 Meyer has been granted a waiver which permits him to
12 participate in all official matters concerning tramadol.
13 A copy of the waiver statement may be obtained
14 by submitting a written request to FDA's Freedom of
15 Information Office, room 12A-30 of the Parklawn Building.
16 In addition, we would like to disclose that the
17 sponsor of tramadol previously provided Dr. Eric Strain
18 with 10 doses of 100 milligram injectable tramadol. During
19 the period of 1994 through October 1995, Dr. Strain and a
20 colleague at Johns Hopkins conducted an investigator
21 initiated study of the abuse potential of tramadol in
22 opioid dependent volunteers. A report of the study
23 findings has not been written.
24 In the event the discussions involve any other
25 products or firms not already on the agenda for which an

1 FDA participant has a financial interest, the participants
2 are aware of the need to exclude themselves from such
3 involvement and their exclusion will be noted for the
4 record.
5 With respect to all other participants, we ask
6 in the interest of fairness that they address any current
7 or previous involvement with any firm whose products they
8 may wish to comment upon.
9 Thank you.
10 I would like to remind everybody to please
11 speak into the microphone whenever you speak. There are
12 floor microphones over there for the sponsor, the podium
13 microphone, and microphones for everybody at the table.
14 Thank you.
15 DR. STRAIN: Thank you, Dr. Templeton-Somers.
16 I'd now like to turn to Dr. McCormick from the
17 FDA for introductory remarks. Dr. McCormick.
18 DR. McCORMICK: Thank you. Good morning. I'd
19 like to welcome the advisors, the sponsors of Ultram, the
20 FDA staff, and the public to the April 28, 1998 meeting of
21 the Drug Abuse Advisory Committee.
22 We've invited our Drug Abuse Advisory Committee
23 to meet with us today to provide guidance to the FDA on a
24 subject of very narrow focus, on the interpretation of the
25 data which have accumulated since the approval of tramadol,

1 approximately four years ago, that pertains to its
2 potential for abuse. We are not seeking advice about the
3 efficacy or mechanism of action of this product as an
4 analgesic. We are not seeking advice about its safety
5 profile. That has been and is currently under discussion
6 with the primary review division. We would like you to
7 limit your focus and discussions only to those factors
8 needed to determine its potential for abuse.
9 During the day, you will recall the types of
10 data which were available for the previous meeting on the
11 subject in 1994, what data have accumulated since that
12 time, and finally the agency's responsibility under the
13 Controlled Substances Act.
14 In order to recall the previous discussion that
15 took place in 1994 by this committee, you were given a
16 transcript of that meeting. Some of you may recall, since
17 you were present then, that there was a great deal of
18 discussion about the fact that this drug had an
19 acknowledged potential for abuse and that that potential
20 was low, although there was very little discussion about
21 what "low" meant relative to other products scheduled under
22 the statute.
23 Preclinical data, which included the metabolic
24 profile, results of binding assays involving both the
25 parent compound and the active metabolite known to be

1 active at the mu receptor and to a greater extent than the
2 parent compound, preclinical abuse liability data, and
3 foreign marketing experience were all evaluated at that
4 time. Available reports from Europe were sparse, and it
5 was thought that tramadol might behave differently in the
6 U.S. marketplace. Nevertheless, a wait-and-see approach
7 was taken.
8 The sponsor had presented at that meeting the
9 concept of an independent steering committee which would
10 monitor for early abuse and recommend intervention if
11 needed. The sponsor will, we hope, today present the
12 parameters that the committee has followed in its
13 surveillance program and intervention.
14 New information is now available on patterns of
15 abuse in the United States, and while abuse remains
16 relatively low, information now exists that should allow
17 this committee to assist the FDA in making a judgment about
18 how this pattern compares to other substances that are or
19 are not scheduled. There are now four years of post-
20 marketing surveillance data from which to draw, all from a
21 variety of clinical sources, including the findings from
22 the independent steering committee.
23 It is not the rule to defer recommendation for
24 scheduling until years after approval, particularly when
25 there's the suspicion of abuse potential. Such decisions

1 are ideally made when the drug enters the marketplace.
2 However, there are historically examples in which deferred
3 scheduling has occurred when data were not sufficient at
4 the time of approval to support a decision for scheduling.
5 This was true in the case of butorphanol and propoxyphene
6 as well.
7 In the case of butorphanol, a more recent case,
8 the FDA was criticized for its failure to adequately warn
9 the public about the potential for abuse and dependence and
10 to schedule the product in a timely manner. In such cases
11 as this, we are led to think very carefully about the
12 message that's communicated when a decision to schedule or
13 not schedule a drug is made. We will revisit this question
14 presently and hopefully throughout the day.
15 In situations where a scheduling decision is
16 contemplated and reviewed by an advisory committee prior to
17 approval and not made at the time of approval, the FDA
18 customarily follows these carefully to ascertain whether
19 there is more of a problem than anticipated. In the case
20 of tramadol, there has been another mechanism in place to
21 screen for abuse, the independent steering committee. We
22 would like to ask this committee to assess whether this
23 kind of approach adds significantly to the routine passive
24 surveillance mechanism that the FDA has in place already.
25 Consider what was the intention of the committee, what

1 questions it set out to answer, how did it accomplish these
2 goals. In particular, did it generate information that
3 would not have been gathered until later and did this
4 information lead to any kind of action?
5 Early in tramadol's post-marketing course,
6 there were reports of reinitiation of abuse, cases
7 suggestive of neonatal withdrawal, and cases of withdrawal
8 and dependence. These reports were sufficient to result in
9 the issuance of a Dear Health Care Professional letter and
10 the addition of fairly strong warnings and precautions to
11 the labeling.
12 I'd like to take a moment, if I may, to provide
13 some clarification on the background material that was
14 provided to the advisory committee which was the eight-
15 factor analysis in draft form and also to give my apologies
16 to the sponsor for any misconception that this document
17 might have created. In the draft eight-factor analysis,
18 there was language to suggest the sponsor has marketed this
19 product in a way that was in conflict with the regulations
20 and their labeling. This is certainly not the case, and
21 insofar as the FDA's Division of Drug Marketing and
22 Advertising and Communications has not to date taken issue
23 with the sponsor's marketing, there's no issue of
24 misbranding. It was not the FDA's intent to convey that.
25 Nevertheless, it is the opinion of the division

1 that the current labeling may perhaps be leading to a mixed
2 message to the public and that's something that we would
3 like you to explore today.
4 One of the tasks before the committee is to
5 examine the new information that will be presented by the
6 sponsor and the FDA, listen to it carefully, understand all
7 of the databases that will be described. As experts, you
8 understand that no one piece of information will allow you
9 to make a judgment. The sources of data are varied. Just
10 as in the metaphor of the six blind men from Hindustan who
11 went to see the elephant, you will be asked to evaluate
12 facets of information and render judgments based on very
13 limited data, none of which provides the whole story. It
14 will be important for you to keep these limitations in mind
15 as you deliberate and discuss these things.
16 The FDA speakers have been urged, in their
17 preparation for this meeting, to explore with you the
18 origins of each of these data sources that they will be
19 discussing so that you know what the limits of the
20 numerator and the denominators are. I would urge you to
21 keep these limitations in mind, and if you do not hear from
22 either the FDA or the sponsor an adequate explanation,
23 please probe until you do. The origins and limitations of
24 these data may not be altogether clear at first blush.
25 One final charge to this committee in

1 evaluating the abuse liability of tramadol is to keep in
2 mind that the statute meant for abuse liability to be
3 considered in a relative sense. There was a great deal of
4 discussion in the 1994 meeting of what significant abuse
5 meant. Keep in mind that the definition of abuse in the
6 Controlled Substances Act is relative, not absolute. The
7 products currently scheduled should serve as a guide to
8 estimating the relative potential for abuse of this
9 product. For example, in schedule 2, are products such a
10 fentanyl, morphine, and oxycodone, whereas in schedule 5
11 are products such as the codeine cough preparations and
12 buprenorphine with a much lower abuse potential. So, these
13 are the ceiling and the floor that currently exist.
14 Take a moment now and then again later to hear
15 what the factors are that have been defined in the statute
16 and after each factor recognize that a comparison is
17 required. And I will just run through the eight factors
18 with you here and you will hear them again throughout the
19 day, and this is from the statute.
20 The first is the drug's actual or relative
21 potential for abuse.
22 Scientific evidence for its pharmacologic
23 effect, if that's known.
24 The state of the current scientific knowledge
25 regarding the drug.

1 Scope, duration, and significance of abuse.
2 History and current pattern of abuse.
3 What, if any, risk there is to the public
4 health.
5 Psychic or physiologic dependence liability.
6 And finally, whether the substance is an
7 immediate precursor of a substance already controlled.
8 Consideration of such parameters as the drug's
9 pharmacokinetic profile, penetration of the blood brain
10 barrier, formulation, route of administration, potency and
11 binding assays, ease of synthesis, degree of trafficking
12 are some of the factors that are taken into consideration
13 in assessing these eight factors and making comparisons.
14 Your charge today will be to consider the
15 available data, the responsibilities under the Controlled
16 Substances Act, and the standards that have been applied to
17 other products. We ask you to apply the same standards to
18 this product that have been applied to others in a fair and
19 evenhanded manner and that at all times you consider the
20 public welfare first above all else.
21 Thank you.
22 DR. STRAIN: Thank you, Dr. McCormick.
23 We will now move to the sponsor's presentation.
24 I have been told that the sponsor has requested that the
25 committee hold off on questions until the end of the

1 presentation. We will take a break part way through the
2 sponsor's presentation. That is all right with you. Is
3 that correct?
4 DR. BURTON: Yes.
5 DR. STRAIN: So, we will begin with Dr. Graham
6 Burton from R.W. Johnson Pharmaceutical Research Institute.
7 Dr. Burton?
8 DR. BURTON: Good morning, Mr. Chairman, Dr.
9 Templeton-Somers, members of the advisory committee, ladies
10 and gentlemen. Allow me to introduce myself. I'm Dr.
11 Graham Burton. I'm Vice President of Regulatory Affairs at
12 the R.W. Johnson Pharmaceutical Research Institute. I'll
13 probably be referring to us as PRI in the future, and you
14 might hear that. And in addition, the marketing
15 organization associated with the research and development
16 group is Ortho-McNeil.
17 As we see from the agenda, we are here to
18 review the scientific evidence surrounding the proposal for
19 the initiation of a scheduling action for Ultram, tramadol,
20 under the Controlled Substances Act.
21 Before I go any further, I'd like to run
22 quickly through the dramatis personae who will be
23 presenting this morning on our behalf to provide you with
24 some of the scientific information that we wish to put
25 before you.

1 This slide shows the first two speakers, Dr.
2 Burks and Dr. Jasinski, and the next slide shows the
3 remainder. The break will occur after Dr. Cicero's
4 presentation describing the results of the independent
5 steering committee's work to date.
6 I also see from the agenda that our colleagues
7 from the reviewing division will present a regulatory
8 history relevant to the how's and why's we have come here
9 today -- and you've heard some of that already -- to review
10 the scientific and medical aspects pertaining to the public
11 health surrounding the availability of Ultram in the U.S.
12 As a result, I'm going to shorten my
13 introduction but wish to remind the committee of some of
14 the key milestones that were associated at the time and
15 around the time of approval of Ultram.
16 Prior to approval for marketing, this committee
17 was consulted, as you have heard, by the reviewing division
18 on the potential for abuse liability, amongst other things,
19 and the majority of members at the time did not think that
20 tramadol had significant abuse liability.
21 At the same time, the committee drafted and
22 voted on another motion. This was that the substance will
23 not be scheduled under the CSA, contingent upon the FDA and
24 the sponsor devising adequate protection for the public.
25 Following the meeting, an agreement was reached

1 with the reviewing division such that adequate protection
2 for the public would be provided. This adequate protection
3 implied two things: that a careful post-marketing
4 surveillance study was to be carried out with a goal of
5 providing an early and sensitive warning system of any
6 abuse of the drug, and that the sponsor would monitor the
7 distribution, use, and promotion of the product in lieu of
8 scheduling it under the Controlled Substances Act.
9 Marketing commenced, following agreement on
10 these issues and others, in March of 1995.
11 Now, for the post-marketing study, the
12 sponsor's commitment was to form the independent steering
13 committee, and this company commitment was to develop a
14 plan for the detection, intervention, and reporting of
15 abuse of Ultram. This study was established and overseen
16 by an independent steering committee whose chairman, Dr.
17 Ted Cicero, is here with us today. But before passing to
18 him, there are some other subjects which are highly
19 relevant to your deliberations today that we would like to
20 bring to your attention.
21 The first of these encompasses the area of
22 pharmacology of Ultram. This committee has already
23 acknowledged that there is more than one mechanism of
24 action of this drug, and we believe that the FDA appears to
25 have had trouble accepting this principle. We have asked

1 Dr. Tom Burks to bring you up to date on this subject, and
2 Dr. Jasinski will also provide some information.
3 Now, for example, I'd just like to point out
4 there have been statements made implying that Ultram is
5 merely a prodrug and that it has only mu opioid receptor
6 activity. This is incorrect. In order to correct any
7 misunderstandings in this context, our first two
8 presentations will address these issues.
9 Now, Dr. Burks will present an overview of the
10 pharmacology of Ultram on behalf of the specially convened
11 independent group of experts who made observations relevant
12 to our discussions today. These concern the mechanism of
13 action and the relevant pharmacology of Ultram.
14 Second, Dr. Jasinski from the Johns Hopkins
15 University School of Medicine will address the issue of the
16 pharmacology of the drug at high dose and its relevance to
17 potential for abuse and how it compares with other
18 analgesic opiates. Being at the sharp end of clinical
19 practice in the field of drug abuse, I feel sure that Dr.
20 Jasinski can contribute significantly to your discussions
21 today, linking the pharmacology of the drug to a clinical
22 practice encompassing patients with serious physical and
23 psychological challenges.
24 Now, following this committee's recommendations
25 in 1994, the FDA were undoubtedly imaginative in allowing

1 the unscheduled marketing of this product whilst
2 encouraging the sponsor to conduct a study to detect and
3 characterize at a very early stage any indications of
4 tramadol abuse. Implementation was aligned with
5 intervention strategies should abuse be identified.
6 Now, the first two speakers are going to lay
7 the foundation for what is probably the most important of
8 our presentations today, that of the findings,
9 observations, and conclusions of this independent steering
10 committee. Dr. Cicero will present those.
11 I wish to also inform you that all but two
12 members of this committee are here today insisting that
13 they attend and will be delighted to be invited to answer
14 questions and be involved in this discussion.
15 Dr. Cicero will describe the unique methodology
16 used in this prospective case-seeking study, the findings
17 of which we believe support the original contention that
18 the risk of abuse of tramadol in the U.S. population is
19 low, reflecting experience gained from over 20 years' use
20 of the product in other parts of the world. Following Dr.
21 Cicero's presentation, I encourage you to ask all the
22 difficult questions that you can.
23 In the complex field of drug abuse, the terms
24 physical and psychological drug dependency are often used
25 interchangeably, but it is more complex than at first it

1 appears as there are factors that need to be borne in mind
2 when calculating benefits and risks to public health.
3 One of these involves the innocent sounding
4 categorization and definition of drug abuse dependence and
5 the related medical terminology and how these relate to
6 what actually happens with patients.
7 The second concerns how reports about patients
8 from professional health care staff and patients
9 themselves, how these become categorized and validated
10 without perhaps the due care and attention that they
11 deserve. There is an irresistible urge to interpret and
12 use such information for the protection of public health,
13 but we must and should recognize how this information is
14 used to achieve both clarity and agreement of definitions
15 and transparency of thought that goes into making
16 recommendations. We need to avoid coming to inappropriate
17 conclusions.
18 The third, of course, is the benefits side of
19 things too. If the patient does not have reasonable easy
20 access to one product, what is the down side with the
21 replacement of one drug by others of similar or, indeed,
22 different mechanisms of action? Would this change
23 standards of care for those who need the drug?
24 Dr. Seddon Savage will bring some balance to
25 the benefits side of this equation with regard to outcomes

1 that may inappropriately be labeled as abuse or dependence,
2 and indeed this is one of the small controversies. Dr.
3 Savage will address the issue of what constitutes physical
4 dependence or withdrawal symptoms and what is psychological
5 dependence and abuse in the context of the clinical use of
6 analgesics in patients with chronic painful conditions.
7 Following on from Dr. Savage, we introduce Dr.
8 Jones. Dr. Jones is an ex-director of the drug safety
9 group here many years ago and has a lot of experience in
10 this area. She will briefly discuss the appropriateness of
11 categorizing anecdotal reports of abuse dependence and
12 other conditions using numbers of reports as an a priori
13 fundamental for regulatory action. The interpretation of
14 clinical trial data is fraught with difficulty. If I may
15 suggest, the data interpretation from spontaneous reports
16 is fraught with hazard. Dr. Jones' comments will, I trust,
17 provide the platform for the appropriate categorization,
18 use, and interpretation of such data and place this subject
19 in context.
20 Finally, you'll have seen a statement before
21 you written by Dr. Portenoy. He is not able to come here
22 today but I would encourage your considerations of his
23 views coming from, as they do, a physician deeply involved
24 with the management of patients with pain, often in the
25 context of very debilitating disorders and terminal

1 diseases.

2 That said, I encourage you to review what the

3 speakers say this morning in relation to the questions

4 before you, and now it gives me great pleasure to hand over

5 to the first of our speakers, Dr. Tom Burks.

6 DR. STRAIN: Thank you, Dr. Burton.

7 While Dr. Burks is coming up, could I just

8 clarify? Are you asking that we hold the questions until

9 the end of the whole presentation, or you suggested we

10 grill Dr. Cicero in particular.

11 (Laughter.)

12 DR. BURTON: Yes. The suggestion is if we

13 could run through our presentation because we need to stick

14 to the time schedules and get the biobreaks in at the right

15 time. I feel that so many questions need to be asked and

16 would be asked, that all that would go through the window

17 and I would get into trouble for exceeding our time limit.

18 DR. STRAIN: That's fine. No problem. Thank

19 you.

20 DR. BURKS: Good morning.

21 An understanding of the abuse liability of

22 tramadol requires some degree of understanding of the

23 mechanism of action, and the fact is that our independent

24 expert panel on tramadol, which reviewed essentially all of

25 the literature available on the subject of mechanism and

1 other actions of tramadol, concluded that tramadol is
2 indeed an atypical analgesic, that it has two modes of
3 action. One of those, and a very important one, is
4 inhibition of uptake of norepinephrine and 5-
5 hydroxytryptamine, or serotonin. The other one involves
6 agonist actions at mu opioid receptors.
7 Both of these actions are important and there
8 is potentiated synergy between these two actions and each
9 potentiates the other.
10 There are also positive multiplicative actions
11 at multiple sites in the body, most especially the spinal
12 cord and the brain.
13 Tramadol is biotransformed primarily in the
14 liver to an M1 metabolite in animals and humans, but humans
15 produce small amounts of M1 relative to animals. And Dr.
16 Jasinski's data will illustrate that point.
17 M1 clearly is more potent than the parent
18 tramadol as an agonist at mu opioid receptors. In fact, if
19 I could have the next slide, we'll see that tramadol is
20 relatively weak as an agonist. It has been best studied in
21 rat brain, although it has also been characterized in
22 cloned human mu receptors.
23 Tramadol is active in the macromolar range at
24 the mu opioid receptors. The M1 metabolite, and especially
25 the positive enantiomer of M1 is relatively more active at

1 the mu opioid receptor and is about one-hundredth the
2 activity of morphine at that receptor. Both of these were
3 relatively less active in the cloned human receptors.
4 In contrast to morphine, though, the inhibition
5 of uptake of monoamines is very striking. There's very
6 little effect on dopamine uptake, but norepinephrine and 5-
7 hydroxytryptamine uptake are both affected by tramadol,
8 with the positive enantiomer being relatively active
9 against 5-HT uptake and the negative enantiomer active
10 against norepinephrine uptake, and again these two actions
11 synergize with one another.
12 The big question before us in terms of
13 mechanism is, is tramadol simply a prodrug for the
14 O-desmethyl tramadol, that is, the M1 metabolite? And our
15 expert panel answered no, and I'll give you the reasons
16 now.
17 The major evidence for a nonopioid component of
18 action is the incomplete reversal by naloxone of tramadol
19 in animal and human studies. Usually naloxone will block
20 only 25 to 50 percent of the effect of tramadol as an
21 antinociceptive or as an analgesic.
22 There is also minimal tolerance or cross-
23 tolerance to tramadol after long-term administration,
24 unlike typical mu opioids.
25 Tramadol is active when little M1 metabolite is

1 formed.

2 And there is blockade of tramadol actions by

3 norepinephrine and 5-HT antagonists.

4 This incomplete reversal by naloxone is very

5 important because naloxone blockade indicates the opioid

6 component of action. If something is not blocked by

7 naloxone, it is nonopioid, and one can engage in

8 speculation about actions, but the proof of the pudding is

9 whether it's blocked by naloxone in terms of whether it's

10 an opioid action or not.

11 Tramadol, as I mentioned, is active in

12 antinociceptive tests even when little or no M1 is formed.

13 For example, in animals when it's injected directly into

14 the specific sites of action and the central nervous system

15 where there is little formation of M1, the tramadol is

16 still active as an analgesic. In animal studies and in

17 human studies, tramadol is active when the liver does not

18 generate significant amounts of M1, whether the formation

19 of M1 is blocked by a drug or whether it is genetically

20 determined.

21 Tramadol antinociception is blocked by

22 yohimbine and ritanserin. These studies have been carried

23 out both in animals and humans, and under the specific

24 conditions of these tests, under parallel conditions

25 carried out at the same time, the actions of morphine are

1 not blocked.

2 We conclude then that tramadol acts by dual

3 mechanisms, a nonopioid mechanism that's mediated by

4 norepinephrine and 5-hydroxytryptamine, plus an opioid

5 mechanism that is mediated by both the parent compound and

6 by the M1 that is formed.

7 Now, we'll carry our discussion on into

8 clinical studies that were conducted by Dr. Don Jasinski of

9 the abuse potential of tramadol. Don?

10 DR. JASINSKI: For about 60 years, we've worked

11 on the abuse potential of mu agonists doing clinical

12 studies. There's a long history of it. In essence, the

13 basis of this in humans that essentially was the basis

14 established in the Controlled Substances Act is

15 pharmacologic equivalence; that is, if the drug has

16 addiction-sustaining, addiction-forming properties of

17 morphine, it's equivalent.

18 In humans, looking for selectivity, the issue

19 was we do studies in clinical analgesia, single-dose

20 assays, getting relative potencies, relative usually to the

21 standard morphine, and giving equivalent doses.

22 Then we conduct studies in substance abusers

23 with histories of opiate abuse, and we do single-dose

24 studies for miosis, pupillary constriction, subjective

25 effects, and euphoriant measures and get again a set of

1 relative potencies.

2 Then we used to do suppression studies in

3 morphine dependence to suppress morphine withdrawal, get

4 dose-response curves, and calculate relative potencies to

5 morphine. And we could also do this in single-dose studies

6 for respiratory depression.

7 And this whole body of data showed that the

8 relative potencies for analgesia and these effects in

9 opiate addicts were quite similar and there was no

10 selectivity, including drugs such as propoxyphene and

11 pentazocine and buprenorphine, which were the drugs which

12 were mentioned. So, there was no evidence of selectivity.

13 On the other hand, we're also concerned by the

14 drug having reinforcing properties from a different

15 mechanism, seeing whether it was particularly euphorigenic.

16 Now, the first study was done about 1990 with

17 my colleague Kenzie Preston and Margaret Testa. The basis

18 of this was that there was about 17 years of marketing in

19 Germany and really at a time when there was a high degree

20 of abuse of mu agonists in Germany, and there was actually

21 very good epidemiologic data from the SAWS data indicating

22 a level of abuse.

23 The question was this pharmacology or was this

24 just not being discovered. There was little or no evidence

25 of any opiate-like effects that were being demonstrated in

1 any humans from any studies which had been available.
2 McNeil was proposing to market in a 50- or 100-
3 milligram dose unit. They eventually settled on the 50-
4 milligram dose unit.
5 There was a preparation in Germany
6 parenterally, and so we did an IM study, intramuscular
7 comparison. The data from Germany suggested that it was
8 about a tenth as potent as morphine when injected, that is,
9 100 milligrams equivalent to 10 milligrams of morphine.
10 So, this was a study which we designed with 30 milligrams
11 of morphine and a top dose of 300 milligrams.
12 The findings in this study were we saw no
13 miosis and no opiate-like subjective effects, no clear
14 indication of any euphoria as measured by our liking and
15 MBG scales. We concluded it had lesser abuse potential
16 than propoxyphene and pentazocine. There was no evidence
17 in the intramuscular studies for any prodrug activity
18 because we saw no opiate-like effects. There was no kappa-
19 like activity and this was not an agonist/antagonist.
20 Now, in this study, the concerns we had were,
21 just looking at this and being critical of ourselves, what
22 if we pushed the dose? Would we see opiate-like effects?
23 Secondly, was this a product just for getting
24 the IM and what we were seeing was perhaps, since we didn't
25 have pharmacokinetics, a depot formation.

1 And thirdly, would we see the prodrug effect if
2 we pushed the dose orally because historically the one
3 prodrug we have, a drug called tilidine which is marketed
4 in Germany -- and that drug is virtually impotent when it's
5 injected -- inactive injected. When you give it orally,
6 it's converted into an opiate.
7 So, we did additional studies. We did an IV
8 study where we compared it to morphine and pushed the dose
9 IV. We did an oral study versus oxycodone, which is the
10 opiate in Percocet, Percodan, Tylox, and it has a fairly
11 high abuse potential. And then we did an oral
12 pharmacokinetic/pharmacodynamic study.
13 I promised Cynthia. What happened was these
14 studies were all completed about four years ago. Now, my
15 friends over here hit a bureaucratic snafu, and this was
16 studied TAD in the series. We did four studies, tramadol
17 abuse, A, B, C, and D. And this is TAD and it never got
18 sent in, the study report to the Food and Drug
19 Administration. So, this is like the judge who tells you I
20 am going to present it, but you're not to consider it in
21 your deliberations. Is that appropriate, Cynthia?
22 DR. McCORMICK: Yes.
23 DR. JASINSKI: Okay.
24 And we did the IV study, and this was to show
25 that my friend, Kenzie Preston, didn't participate in the

1 rest of these studies. She became a fed. She's now at the
2 National Institute on Drug Abuse. And my colleague John
3 Sullivan.
4 Our traditional was to infuse the drugs. We do
5 this with cocaine, most drugs, using a pediatric infusion
6 pump over 1 minute. We got up to 700 milligrams with no
7 particular opiate-like effects, and we saw a seizure. Now,
8 what was interesting was the seizure occurred during the
9 infusion. So, it's immediate. So, the seizure activity is
10 with the parent compound and it was not opiate-like.
11 So, clinically what you do is if you want to
12 lower the effects, you slow down the infusion rate, the
13 difference between giving a drug like this and giving it
14 slowly. So, we went to 2.5-minute infusion, and we got a
15 seizure with 300 milligrams, again immediate.
16 So, we went to a 5-minute infusion for all the
17 drugs with the 200 milligrams and compared it to 10. So,
18 we're still in the 10 to 1 ratio for comparison.
19 So, this is the final study which we did, and
20 these were the four drug comparisons.
21 Now, if you're into analgesia, one of the
22 questions is measuring onset. We had the staff asking them
23 every minute after completion of infusion, how much do you
24 feel the drug? This being placebo, which they didn't feel,
25 and this being the 20 milligrams of morphine. The point I

1 want to make is that the effects of tramadol come on very
2 rapidly. This is consistent with what we saw, that the
3 subjective effects -- there is a discrimination which
4 occurs very rapidly with the tramadol. So, it's not
5 circulating with producing a prodrug. So, we think this is
6 probably the parent drug.
7 This is the time course over 12 hours of how
8 much do you feel the drug. No. They screwed this up. I'm
9 sorry. They got the labels wrong. They remade my slides.
10 This is pupillary constriction, and what you'll
11 see is that pupils constrict. This is placebo and you'll
12 see that there's dilation from the tramadol. So, there's
13 no constriction with the 200 milligrams. This is what
14 we've seen usually with -- probably due to the serotonergic
15 uptake activity. A consistent dilator of pupils has been
16 serotonergic activity.
17 This is how much do you feel the drug. Again,
18 you'll see the time course is very similar. They do feel
19 it. This is not a euphoriant and it's not morphine. They
20 didn't like it. This is plus or minus one-half the least
21 significant difference, and this shows statistical
22 difference and the degree of separation gives you an
23 estimate of the observed power. And you'll see they really
24 didn't like tramadol, nor did it produce an MBG response.
25 So, it's psychoactive. There were effects there. They

1 detect it. It's not dope.

2 The oral study compared it with 20 and 40

3 milligrams of oxycodone. This is equivalent to about 20

4 milligrams of morphine. This is eight Percodan tablets.

5 175, 350, and 700 milligrams of tramadol. This is 14

6 tramadol tablets, just to put this in somewhat perspective.

7 We were pushing the dose higher, and I think at 750

8 milligrams in the dose-ranging study, we saw a seizure,

9 which is about 15 tablets.

10 If you look at this, you'll see again this is

11 the oxycodone constricts pupils. The tramadol initially

12 dilated pupils, then had a slow pupillary dilation. When

13 you have disparate time course curves, my friend, Mike

14 Klein, doesn't like us to use area under the curves, so we

15 agreed on using the maximum response. This is the maximum

16 constriction from baseline. Again, you'll see that

17 oxycodone constricts pupils and that the tramadol also

18 constricts pupils. And this is the mean maximum change.

19 You also can take the time of this maximum

20 change and calculate when this occurred. We see a very

21 interesting phenomenon. Oxycodone is very rapid and you'll

22 see that there's really no difference, and this is

23 pharmacologically. The time of maximum response or plasma

24 concentration is independent of the dose. What you'll see

25 is that the maximum pupillary constriction occurs at about

1 9 hours. I've never seen this before, pushing the dose and
2 one gets it.
3 This is "feel the drug" maximum, and you'll see
4 again that this is about an hour to 2-hour delay coming in
5 lately. So, when you push the dose, it occurs much later.
6 I've never really seen this in any particular drug before.
7 Well, these late occurring effects, which occur
8 late, are typically opiate-like. Subject identifies an
9 opiate. There's an MBG response, a liking response. And
10 this again is just showing you, for example, the liking
11 scale, the maximum. And this is the time which is late
12 occurring, and all of the others look like this. It really
13 occurs an hour or 2 hours later. So, it's not minutes.
14 It's hours difference when this starts occurring.
15 Now, the metabolite issue. This is the last
16 item. This is the study you haven't seen which was done
17 five years ago. So, it's not there.
18 Is tramadol a prodrug? Simply we looked at
19 this, we said, aha, what we're doing is producing a
20 metabolite which is coming on slowly reaching peak
21 concentration. A nice, simple explanation.
22 Well, we did another study with 6 subjects and
23 we did the same measures with 100 and 400 milligrams of
24 tramadol. Again, we saw the same phenomenon, initial
25 pupillary dilation, late-occurring, opiate-like effects.

1 This is the tramadol plasma levels for the two
2 doses, and this is the M1 plasma levels. Again, you'll
3 see, just consistent with the preclinical and my friend
4 Tom, is that the production of the M1 metabolite is much
5 less in humans than in animals. It does occur.
6 Now, if you're into pharmacokinetics, you can
7 look at the Tmax and the half-life. The Tmax, the time of
8 maximum concentration, for the tramadol and the M1 for the
9 doses are virtually on top of each other, and the half-
10 lives are not really significantly different.
11 So, this issue is this appears in plasma with
12 the liver. It appears very fast, but it doesn't correlate
13 with the pharmacodynamics. So, this is not a simple
14 explanation of a simple oral prodrug. It doesn't look like
15 tilidine, for example.
16 No opiate-like effects in IM or IV studies. We
17 couldn't demonstrate even pushing the dose to our maximum.
18 The oral studies. The delayed opiate-like
19 effects. I'm not really sure this is just a simple
20 explanation of the production of a metabolite. We really
21 can't make that argument. You only see these opiate-like
22 effects in larger doses. Again, being consistent with the
23 preclinical pharmacology, we see a mixture of opiate and
24 nonopiate-like effects. And it's also consistent probably
25 that in the therapeutic the opiate-like effects aren't seen

1 and what you're producing in the analgesic, the therapeutic
2 doses, is analgesia through a mechanism other than the mu
3 agonist.
4 Conclusions. This was originally the
5 conclusion from this data five years ago. It had a lesser
6 abuse potential than propoxyphene or pentazocine because
7 these drugs clearly where you can inject them
8 intravenously, IM produce opiate-like effects.
9 Therapeutic effect was nonopiate-like, whereas
10 with propoxyphene or pentazocine, these are clearly mu
11 agonists. There's no evidence of selectivity.
12 We do have a clear evidence from a dissociation
13 when you look at the clinical analgesia and the opiate-like
14 effects. At that time, we felt that there was really, in
15 conjunction with the SAWS data, which was the determinant
16 factor, no real pharmacologic basis to argue for control
17 under the Controlled Substances Act.
18 Now, I introduce my esteemed colleague, Dr.
19 Cicero, who's Chairman of the independent steering
20 committee.
21 DR. CICERO: I'm glad to be here. You're going
22 to ask me all the tough questions. I understand it and I'm
23 happy to do it.
24 Tramadol again was approved by the FDA as a
25 non-scheduled drug in 1994. The Drug Abuse Advisory

1 Committee made a recommendation that it be not scheduled in
2 1994. The most important evidence that led to that
3 decision is shown on the next slide.
4 First, it was the European experience with
5 tramadol which suggested a very low abuse potential.
6 Indeed, the only data we had available was from tramadol
7 being marketed in 70 countries overseas with about 20
8 million patient exposures, and there was a rate of around
9 200 to 300 patients who appeared to experience some
10 difficulty with tramadol abuse, leading to a rate of about
11 1 to 1.5 cases per 100,000 patients exposed.
12 That number seemed a bit low to us but it was
13 the only number we had available to us at the time,
14 projected from the European literature. The experience in
15 this country may well show a rate around that level.
16 We also argued, I think rather effectively,
17 that there was a risk-benefit analysis here, that
18 scheduling drugs had a definite impact on physicians'
19 prescribing practices, and in fact contributed to the
20 undertreatment of pain in this country. Therefore, if we
21 could have a non-scheduled compound with an acknowledged
22 but low abuse potential under certain conditions, this
23 would actually be in the interest of public health.
24 The DAAC I think, though, correctly believed
25 that the drug should only be non-scheduled if there was

1 some sort of a safety net established. Now, what did it
2 mean by a safety net? I think there was some general level
3 of distrust about European data, definitions of abuse,
4 whether the experience in this country will be different
5 than that which is observed in this country only because of
6 a culture that may take more drugs. We define substance
7 abuse a little bit differently here. There was this
8 concern that with a compound, a weak opiate, a compound
9 being released, that we might see unbridled drug abuse
10 throughout the country. There was a deep concern about
11 that issue.
12 The company committed that it would market
13 tramadol appropriately. What do we mean by that? They
14 stressed that tramadol had low abuse potential, not no
15 abuse potential. That had to be a clear message. None of
16 its promotional material could in fact tout the non-
17 scheduled benefits or status of tramadol. It had to be
18 marketed in that fashion.
19 They had to, secondly, though, undertake a very
20 aggressive, proactive post-marketing surveillance program.
21 Now, what do we mean by that?
22 The current systems in place, such as DAWN,
23 which you'll hear about a little bit this afternoon, are
24 entirely passive, they're retrospective, anecdotal in
25 nature, and most importantly, they're not timely. A big

1 concern that the DAAC had at that particular point in time
2 is what if we release this compound as a non-scheduled drug
3 and a big problem of abuse occurs? With DAWN, the 1996
4 data aren't even published yet. We wouldn't know that we
5 had an abuse problem until a year, year and a half later.
6 Clearly, something much more proactive had to
7 be developed that neither relied on spontaneous reports or
8 on the DAWN system. Clearly, this required an active
9 elicitation of case reports. There had to be a proactive
10 nature to go out there and see is abuse occurring. Is it
11 occurring in a timely fashion? In other words, can we
12 discover when abuse occurs? If we can discover when abuse
13 occurs, can we characterize that level of abuse and can we
14 then develop some sort of intervention program to move in
15 and effectively try to reduce that abuse rate?
16 To do this, of course, we had to be able to get
17 the abuse narrowed to regional levels and in fact to five-
18 digit ZIP codes. We had that degree of power to be able to
19 say, we know where this drug is being abused and in what
20 particular ZIP code it's being abused. This was critical
21 for us to be able to get an idea of whether there was an
22 early penetration of this drug into the marketplace and
23 into the populations so that we could come back.
24 And our charge again, as the independent
25 steering committee, was that it was our trust to you that

1 we would inform you. Should the data indicate that abuse
2 rate was very high and unexpectedly high with this drug, we
3 would immediately and simultaneously notify the FDA and the
4 sponsor that the drug should be scheduled. That was our
5 commitment at the time.
6 As I mentioned, we developed the intervention
7 strategies, and frankly the most important point, though,
8 was this appointment of an independent steering committee.
9 I had served as chairman of the Drug Abuse Advisory
10 Committee for a number of years prior to getting involved
11 in this, and we had had a number of occasions where
12 sponsors had promised to conduct post-marketing
13 surveillance programs and simply had not followed through
14 on it. And in some cases there was some suspicion about
15 how the data were being interpreted.
16 An independent steering committee was charged
17 and the committee agreed to this charge, that we would
18 oversee the promotional aspects of this compound to make
19 sure it was being promoted appropriately, and would be
20 given all the resources necessary to carry out the last
21 three points that are mentioned on that slide.
22 Here is the independent steering committee. I
23 served as Chairman of that committee for the last three
24 years. Dr. Edgar Adams, who's sitting in the front row
25 here. Why don't you just raise your hand as I call upon

1 you? Anne Geller, also sitting in the front row. Jim
2 Inciardi, also sitting in the front row. Alvaro Munoz from
3 Johns Hopkins sitting in the front row. Dr. Schnoll is
4 unable to be with us today from MCV. Dr. Senay sitting
5 right up here as well, and Dr. George Woody, who also could
6 not be with us today.
7 The committee is here I think to lend support
8 to an effort that has occupied an enormous amount of our
9 time and our energy in terms of developing the program and
10 analyzing the data over the last over three and a half
11 years now actually developing the program.
12 Let me try to go through the program as we
13 describe it, and for the sake of full disclosure, I want to
14 indicate obviously these were very, very expensive studies.
15 The company has paid for all of the expenses associated
16 with the conduct of these studies. They are extremely
17 expensive.
18 Even going further with disclosure, some
19 members of the committee received consultant fees as a part
20 of this activity. So, I think that should just be out in
21 the open. This is an independent steering committee, but
22 those are the parameters around it.
23 Here's the overview of the post-marketing
24 program we put together. There are two phase IV studies
25 that are currently underway, and you will not hear any

1 discussion of those today because they are still in
2 progress and we have only basically preliminary data
3 available in one of the two studies. The other is still
4 underway.
5 We had this long discussion, as you will
6 recall, at the 1994 DAAC meeting about what were the
7 appropriate sentinel populations to study in these focused
8 phase IV studies. We ended up with pain patients because
9 we felt this is the population for which this drug is
10 intended. So, if we're going to look for abuse anyplace,
11 we ought to at least look for abuse in this population
12 because, again, it's the group presumably for which there
13 will be the greatest exposure. So, if abuse is going to
14 occur, we certainly want to monitor whether it will occur
15 in this population. We frankly doubted we would see very
16 much in this population because pain patients simply don't
17 abuse their medications, but this study is underway.
18 We also picked impaired health care
19 professionals as a target group, one target group for a
20 very focused study, to see whether we could, in fact,
21 examine systematically in a scientific way whether impaired
22 health care professionals showed an unusually early
23 penetration -- or tramadol did -- into this population for
24 abuse.
25 Why impaired health care professionals? Ready

1 access to drugs. It was a non-scheduled compound which was
2 well aware to them. There were no restrictions on those
3 sorts of requirements.
4 In addition, the original label could not
5 specify, for a variety of reasons that are not quite clear
6 to me, that there was a routine urine screen available.
7 The independent steering committee at the time howled that
8 this ought to be changed. The label ought to indicate that
9 there is a urine screen because it was an open invitation
10 for people to try to sample the drug if they felt they
11 could not be detected. For whatever reason, the original
12 label still does not carry a warning on the urine screen.
13 So, again, we felt for physicians enrolled in treatment
14 programs, the absence of a urine screen and ready
15 availability would make this an ideal population to
16 examine.
17 These two studies, as appropriately pointed out
18 by the DAAC at the last meeting, are not enough. It was
19 focusing on two relatively small populations of people. It
20 ignored -- the much larger issue is if this is a nationwide
21 problem, these two studies aren't going to solve that
22 problem. There were 4,000 or 5,000 patients total
23 enrolled. We needed to get some national surveillance
24 program that would help us elicit these cases.
25 What have we done? This is a program that we

1 developed. Proactive surveillance techniques. One, we
2 monitored tramadol sales, distribution, and physician
3 prescribing practices, including pharmacies, down to the
4 ZIP code.
5 What was our purpose there? We wanted to make
6 sure it was being marketed responsibly. Plus we have the
7 ability to see whether there are any true outliers, and it
8 says is any region of the country selling
9 disproportionately large amounts of tramadol, is any
10 physician prescribing unusually large amounts, i.e., a
11 script doctor? We had a great capacity to get actually in
12 there to analyze the patterns of use of tramadol and again
13 by the three-digit ZIP code level in this case, and there
14 are 897 three-digit ZIP codes.
15 We also -- again, the proactive nature -- went
16 out and solicited and evaluated all case reports that were
17 suggestive of abuse. Now, there clearly are two sources of
18 reports: spontaneous reports that come from the sponsor
19 via the Medwatch system or the FDA and actively elicited.
20 And I'll focus on the actively elicited in a second. Both
21 of these formed case reports that we will now subject to
22 scientific evaluation, and I'll get to that step in a
23 second. But this is probably the key element of our
24 program to this point.
25 One of the most important elements was the

1 proactive surveillance of 110 NIDA grantees who Dr. Leshner
2 and the NIDA branch chiefs eagerly agreed to participate in
3 this study from day one, and in fact had agreed to serve on
4 the committee as a liaison member, and I'll get to that in
5 a second. They made available to us all 110 grantees who
6 had programs in place to study at-risk populations in their
7 particular cities and all of them added Ultram to their
8 battery of drugs that they looked at as part of their
9 surveillance effort. So, this was a key important element
10 for us.
11 We felt we needed, though, more information
12 beyond that because not all these NIDA grantees covered the
13 waterfront. We needed to have other people, sort of key
14 informants. We used that term. That term is borrowed from
15 the epidemiological literature. It is basically someone
16 who is knowledgeable about drug abuse patterns on the
17 street. We were not meeting people under lights in alleys
18 and paying off. That type of informant we weren't using at
19 all. I want to make that quite clear.
20 We identified 145 of these key informants who
21 are directors of methadone clinics, drug-free treatment
22 programs, others that were knowledgeable about drug abuse
23 issues in their local communities. We attempted to blanket
24 the country and get good coverage across the country
25 because we had no idea where to predict that abuse might in

1 fact break out.

2 This is the geographical distribution of the

3 NIDA and the grantees.

4 This is the key informant network, again 255

5 people, overlapped rather heavily in some areas, and it's

6 not quite clear why we ended up with so many in New Orleans

7 and other areas.

8 Again, there was some rhyme to our selection

9 here. We did certainly want to hit areas in which heroin

10 and other opiate use was quite prevalent. The Northeast

11 Corridor was blanketed because of the profile of this drug,

12 but in addition, we wanted nationwide coverage because we

13 had no idea what pattern of abuse might emerge with this

14 compound. I believe we have informants in all of 46 or so

15 of the states. There's a couple that we don't have an

16 informant in.

17 In addition to these methods, we also surveyed

18 high use pain specialists. I should say Ortho-McNeil on a

19 regular basis screened these high pain specialists to see

20 whether they were uncovering any evidence of abuse.

21 We also again, though, used I think number 5, a

22 very important one, Internet surveillance techniques. I

23 had a screen name, which I assure you was anonymous, and I

24 told my university I was using it as an anonymous screen

25 name, to actually go into the Internet. There are about 15

1 to 20 bulletin boards that refer specifically to
2 recreational drug use and many more chat groups that one
3 can go in and actually monitor the recreational use of
4 drugs.
5 In a very short period of time -- and I'll give
6 you some of this data later on -- tramadol appeared within
7 one week of its appearance on the market. Discussion of it
8 began occurring on the Internet about a new drug. There
9 was a new prescription drug out. They had the name wrong.
10 They misspelled it. There was all sorts of things, but
11 within a week I was impressed. The pharmacologists on
12 these things were superb. They had the pharmacology down.
13 It was down completely. The comments were sort of
14 interesting. We'll get into a couple of them. In essence,
15 it was pretty useless except that it alleviated pain was
16 the primary summary that we got from these. Very
17 important, though.
18 Through my screen name, I was actually able to
19 go in and communicate with these people and get additional
20 data if they claimed abuse or they claimed mood-altering
21 effects, and actually was then able to generate a case
22 report off the Internet, which I think is sort of a unique
23 way of using the Internet and showed us adapting to that
24 situation.
25 All cases are evaluated to see if DSM-IV

1 criteria for abuse and/or dependence are met. I'm assuming
2 everyone knows what the DSM-IV criteria are. They're in
3 the report. If anybody wants us to go over them, I will
4 but I'm assuming you all know what the DSM-IV criteria are
5 and I don't mean to insult you by making that comment. If
6 anybody does have a question, though, please ask it.
7 We then rated every case report. Now, what do
8 I mean by a case report? That could be an Internet source.
9 That could be coming from Ortho-McNeil. It could be coming
10 through Freedom of Information from the Food and Drug
11 Administration, and most importantly, our key informant
12 network.
13 As I received reports from the key informants,
14 I called them and otherwise contacted them and got as much
15 information as I could, prepared a case report, and then
16 submitted that case report to a subcommittee of the
17 steering committee chaired by Dr. Senay, who would then
18 rate. Three of them would rate. Drs. Geller, Woody, and
19 Senay would rate the cases as to whether they satisfied the
20 criteria for DSM-IV according to these criteria up here.
21 In addition, on a weekly basis, I generated
22 what was called a C series, for very cleverly Cicero
23 series, of reports that were coming through these networks
24 and submitted them to the company with directions to make a
25 Medwatch form and get them to the FDA. So, the FDA was

1 getting monthly updates on the committee reports as they
2 were being generated, a very important point.
3 Case reports for abuse were either positive;
4 that is, they met the DSM-IV criteria. They were possible;
5 that is, they met some of the criteria for abuse but were
6 not completely positive in that sense. We've elected in
7 all of our studies to pool positive and possible together.
8 Again, we wanted to be as conservative as possible and went
9 ahead and listed. Even if only two of the criteria were
10 met, we included those as a positive case of abuse.
11 Alleged abuse is typically when particularly
12 some health care professional, in the addiction medicine
13 specialties in particular, indicated that he felt one of
14 his patients was addicted, but there was no evidence that
15 we could see that any of the criteria for DSM-IV were met.
16 We believed we still had to count that as an alleged case
17 of abuse because this is an expert, a health care
18 professional who believed that to be the case. So, we
19 called that alleged because it clearly didn't meet the
20 criteria, and there were a lot of reports that something
21 was alleged, a pharmacist alleged I've got someone who's
22 abusing Ultram and there wasn't much more left in the
23 report. Many of our reports have that sort of flavor.
24 Negative refers in this case to negative for
25 abuse in this particular designation.

1 And then finally, withdrawal or physical
2 dependence, and we would prefer the term withdrawal. We
3 have separated this out, and I know this will be a matter
4 of significant debate, but let me put it quite simply.
5 While withdrawal is one feature of DSM-IV and it is
6 certainly in some cases a part of drug abuse, it is
7 certainly not causally related to abuse and withdrawal per
8 se can simply not be considered abuse. It is a serious
9 mistake. It is one of the criteria and I think one of the
10 problems with the Controlled Substances Act is requiring
11 that physical dependence be counted as abuse. It clearly
12 is inconsistent with modern, state-of-the-art principles
13 and validation of drug abuse. Physical dependence is
14 simply not abuse, and we will discuss that more as we go
15 along.
16 I do understand, though, the reasons that the
17 FDA tracks physical dependence and withdrawal, but I would
18 suggest to you and the committee suggests to you it is of
19 no predictive value for abuse and I think is potentially
20 misleading and is probably not in the long-term interest of
21 the public health because most of these cases are patients
22 who have been taking Ultram at rather high levels and
23 physicians withdrew them very quickly and they experienced
24 a mild withdrawal syndrome. None of that led to subsequent
25 drug-taking behavior. It is inconceivable that that is

1 counted as a case of abuse. That has been the status of
2 it.
3 Most importantly, to get to the risk-benefit
4 analysis -- and again, if we go back to the DAWN or the
5 spontaneous reports, there is no ability to estimate the
6 denominator in that case, how many people are exposed. All
7 we get is raw number of case reports. How do we then
8 evaluate a raw number of case reports? What does 200 case
9 reports mean if a drug has 30 million prescriptions written
10 as opposed to 1,000 prescriptions written? I would suggest
11 to you the rate at which one sees the occurrence of events
12 is far more important than the actual raw number alone,
13 just to make those comparisons.
14 But really again, our whole purpose here today
15 -- and I think Dr. McCormick's slide was an excellent one
16 showing the balance. We're trying to balance risk benefit
17 here. The whole Controlled Substance Act, all eight
18 factors, are trying to do that.
19 The risk, of course, is abuse. The benefit, of
20 course, is patients benefiting from that. Throughout all
21 of this analysis that we have to look at that risk-benefit
22 ratio and really the rate of abuse gives us a better
23 approximation than simply raw numbers. So, we're looking
24 at rate of abuse at all aspects today.
25 The committee, as outlined in your handout, has

1 developed a method to calculate patient exposures which is
2 based principally on number of people exposed as opposed to
3 prescriptions and other methods used. That is again
4 outlined in your report.
5 Through December 31st of 1997, we estimate
6 16.5 million people have been exposed to Ultram total. If
7 you use the company's estimates, which had been used
8 traditionally for some period of time, that number is
9 slightly higher, about 18.6 million. If you use -- what is
10 it? PM? I'm blocking on the other source of data.
11 VOICES: IMS.
12 DR. CICERO: IMS. Sorry. That number is
13 around 16 million. Our method gives essentially the same
14 denominator, so there should be no dispute about the
15 denominator here. The range of 16.5 million is a pretty
16 good number. We believe our method produces a, I think,
17 more scientifically valid data, of course, and we could
18 discuss that at some point later down the road.
19 To this date, through December 31st -- and I
20 can only give you data definitively through December 31st
21 because we are at a quarterly survey right now of our
22 informants with a due date of April 31st -- or April 30th.
23 How many days are there in April? 30?
24 (Laughter.)
25 DR. CICERO: Okay. Hey, I'm not a

1 mathematician. I don't know my months as well, either.
2 Through that date, we have 247 cases that are
3 positive or possible for abuse. These are diagnosed cases
4 of abuse.
5 Out of 16.5 million patients, it comes out to
6 be 1.5 cases per 100,000 patients from the date of launch
7 of this drug. Remarkably, as you recall back in August of
8 1994, we made a prediction based upon European data that we
9 were even very skeptical about, that the rate would be
10 between 1 to 1.5 per 100,000. It appears remarkably
11 uncanny that the number that we are getting with actual
12 data over time seems to confirm that.
13 But what these data don't show are the trends
14 in data over time. Are we seeing just a consistent level
15 of abuse or has something changed over time?
16 This gives a plot of the number of patients
17 exposed -- now, this is the denominator -- exposed per
18 month from the date of launch. You can see that it was a
19 couple of weeks that tramadol sales were low, and it really
20 has increased rather substantially over this period of
21 time. It is now averaging around 800,000 people exposed
22 per month.
23 In most of the data I'll be expressing today,
24 we actually calculated the data per month, but then average
25 it and come up with a quarterly composite figure. What I'm

1 showing you is this is the level of patient exposure that
2 we are seeing. It looks as if that has leveled off at some
3 point, although I don't know whether that's meaningful or
4 not.
5 Now we'll look at the rate of abuse by quarter
6 from the date of launch of this drug through December 31st
7 of 1997. I am sorry for the background here. It was
8 supposed to be blue, but it turned out some other color.
9 Before we look at this intensively, let me
10 point out you're going to see two lines in every single one
11 of these graphs. This line, all reports, consists of
12 spontaneous reports from Ortho-McNeil, anything we may have
13 gotten from the FDA, and committee generated reports.
14 Remember now, we are actively soliciting case reports.
15 This line, the blue line, in all these graphs
16 represents, if we subtract out the committee contribution
17 of case reports, what would we have seen if only
18 spontaneous reports, which is the common system used for
19 all others -- that's the Medwatch system -- what if that
20 had been used?
21 The difference between these two lines clearly
22 gives you some indication of how much has the committee
23 contributed to the generation of positive case reports. I
24 should say this is positive case reports that we're talking
25 about. I noticed this afternoon there's an assertion that

1 the steering committee has only contributed 16 percent of
2 the cases of abuse, and I think I have the reason for that
3 because clearly our number is much greater than 50 percent,
4 but this is positive cases of abuse.
5 What you can see, though, rather clearly is
6 nothing much occurred for the first 6 months after the
7 introduction of tramadol onto the market, but then there
8 was, in fact, an upsurge, reaching a peak of about 2 cases
9 per 100,000 in the early part of 1996. Since that time, it
10 has declined over time, and you can see the actual numbers
11 of cases of positive abuse across the top here. It has
12 declined over time to less than 1 case per 100,000 patients
13 with this one blip occurring in the third quarter of 1997,
14 and 12 of those 17 cases occurred in one area, New Orleans,
15 which we'll discuss in a few minutes.
16 It gives an idea, I think, of the sensitivity
17 of the system that we are seeing so few cases, but we can,
18 in fact, get it down to several neighborhoods in the New
19 Orleans area where an outbreak apparently of
20 experimentation occurred, and this accounts for this tiny
21 blip that occurs there.
22 If you look at the worst case scenario now --
23 this is just positive cases of abuse -- what if we look at
24 positive, possible, and alleged, that category I mentioned
25 to you earlier where just someone alleged that abuse

1 occurred, what would that look like? And that's shown on
2 the next slide.
3 Again, same identical pattern occurs, the
4 curves are the same again, showing this enormous
5 contribution by the committee-generated reports. I think
6 the timing is somewhat different. The peak, of course, was
7 3 instead of 2, but really we're down to a level of 1 to
8 1.5 cases per 100,000, even including the alleged category
9 of abuse in that scenario.
10 I think what we interpret these data to
11 indicate quite clearly is a period of experimentation
12 clearly has occurred, and you'll see some maps of the
13 country showing you I think that in a little bit. It's
14 transient use and there appears to be some experimentation.
15 It's our conclusion at this point that experimentation is
16 pretty much over and we're at some stable level. It's hard
17 to say, without continuing this study further, how stable
18 that will be, but it appears that we have reached some
19 stable level.
20 But again, I think looking at just total
21 numbers from data launched is very misleading and not
22 giving us the true pattern. One of the factors, of course,
23 of the Controlled Substances Act that Dr. McCormick
24 reviewed was what is the pattern of abuse? Is it
25 persistent abuse, sustained abuse? I think the answer to

1 that question is clearly no on that level. That is
2 certainly our experience of late.
3 We also, though, do realize that the FDA has a
4 great deal of difficulty understandably in estimating what
5 the denominator is, and much of the data presented are
6 cumulative numbers of cases of abuse from data launch or
7 number of cases per quarter. So, we've actually plotted
8 the data that way. We do not think this really is in the
9 interest again of public health because it doesn't give an
10 indication of risk-benefit analysis, and I don't know how
11 to compare a gross number, a raw number, of cases occurring
12 with Ultram to something else and come up with anything
13 meaningful when the denominator is different. But
14 nevertheless, those data are shown on the next slide.
15 This is the cumulative number of abuse or
16 dependence cases. We have 247 cases, as mentioned earlier,
17 coming from all sources. Less than half of those actually
18 came from the Ortho-McNeil at this point. 52 percent of
19 the cases are now originating from the committee, and over
20 time, as you'll see in subsequent slides, that percentage
21 is growing to the extent the last couple of quarters two-
22 thirds of all positive cases of abuse have been derived
23 from the committee. Spontaneous reports are dropping off,
24 as one would predict, but actively elicited cases are still
25 being reported.

1 This just gives you the quarterly numbers, the
2 same data you saw before, but this is now just the raw
3 numbers. Again, you can see this impact of New Orleans
4 occurring. Clearly, though, the pattern is the same: the
5 period of experimentation beginning 6 to 9 months
6 afterwards, appeared to reach a peak and has now come down.
7 I think if you look at spontaneous reports
8 alone, this drop-off has never been understandable. We
9 don't know whether that means that the problem is actually
10 evaporating or people are just now not reporting it. It's
11 a common feature with spontaneous reports that they drop
12 off over time. That's why we don't see a lot of mentions
13 of morphine in the DAWN database. No one reports that
14 anymore. Not DAWN, but in the Medwatch database. People
15 don't report it anymore. There is a fall-off in
16 spontaneous reports. Clearly, that can't explain what
17 we're seeing here because we are actively soliciting cases
18 throughout this period of time. So, the drop is in fact a
19 real drop during that period of time.
20 The stratification of tramadol abuse by ZIP
21 code. Now, I mentioned we go down to the five-digit ZIP
22 code to be able to trace each one of the positive cases and
23 see what areas of the country in fact are showing us
24 problems.
25 Now, each month the committee meets, we look at

1 the data, we see which areas have an over-representation of
2 abuse cases and make a number of determinations about
3 intervention, which I'll go over in a minute. But they
4 consists generally of us obtaining more information,
5 conducting eight site visits to date to the actual area
6 where we could interview the informants, interview on a
7 number of occasions the actual patients involved and
8 actually get their experiences with tramadol, and then
9 undertake in a number of instances some rather aggressive
10 intervention techniques. Those were our three pledges to
11 this committee we made four years ago that this is what we
12 would do.
13 You're going to notice, as you go through that
14 -- I'm going to go through these very quickly and you've
15 got them in your folder. That's why I'll go through them
16 quickly. You're going to see areas that appear and
17 disappear. They appear rather quickly. All of a sudden
18 you'll see a large number of cases appear, 10 to 12 cases
19 appearing in Madison, Wisconsin, for example, or New
20 Orleans. It's gone the next month. It comes and goes.
21 Our informants tell us it was unsuccessful experimentation.
22 Street addicts tried it. Someone got a bottle. Someone
23 tried a new, novel way of doing it. They found it not
24 satisfactory, dropped it very quickly. We keep following
25 those informants over time to make sure that they're

1 tracking the same patients and can tell us that street
2 addict is no longer taking this drug because it was
3 unsuccessful experimentation, so we can follow through on
4 it.
5 In a number of other cities, as we go through
6 it, we did identify a more substantial problem, and that
7 is, people with a known history of abuse appear to be
8 receiving tramadol as a non-addictive pain reliever. Now,
9 that misinformation has one of two sources, either the
10 sales force was not conveying the appropriate message or
11 the physicians simply weren't hearing the message. One of
12 those two had to be the case because that is not the label
13 indication for tramadol, and that was an area that we could
14 intervene.
15 But very quickly I want to just run through the
16 slides just to give you an idea of the
17 appearance/disappearance. It gives I think a good graphic
18 example that we have not seen sustained use of Ultram
19 across the country for its euphorigenic properties. We
20 simply have not seen that.
21 The other most noteworthy pattern of this is
22 look in the northeast regions, southern Miami, Detroit,
23 Chicago, Los Angeles, where there are large areas in which
24 heroin use and street use of drugs is quite prevalent. You
25 don't see much abuse of tramadol occurring in those areas

1 which we think suggests it is not a very good substitute
2 for that.
3 Can we just run through these really very
4 quickly? You'll just see cases appear. This is by
5 quarter. You can see what occurred all of a sudden in
6 Madison, Wisconsin, in the third quarter of 1996. A "huge"
7 outbreak, 6 or 7 cases occurred in the Madison area at that
8 time.
9 Let me give you an example of the intervention
10 we employed at that point. Ed Senay and I went into that
11 area immediately and contacted five of our informants at
12 the University of Wisconsin and others that we knew to say
13 we've just got a report of I think 8 or 9 -- I can't count
14 that number, but there are 9 cases occurring in the Madison
15 area. Help us out. What's going on up there?
16 Every one of them got back to us and said we
17 think it was an isolated incident on State Street. My
18 daughter goes to Wisconsin. Lots of things happen on State
19 Street in Wisconsin. There seemed to be a sudden use of
20 tramadol. Someone got a hold of some tramadol and some
21 addicts tried it on the street.
22 Since that time, third quarter of 1996, over a
23 year now, we have no further reports from the Madison area.
24 Again, I think our only conclusion can be -- and we're
25 tracking that population -- whatever occurred there is

1 over. It's dissipated. Our interpretation was it was
2 experimentation that was apparently not very successful and
3 went away.
4 Let's go on now. Very worrisome, all of a
5 sudden we got 5 cases from San Francisco. That is an area
6 where we would expect to see some abuse occurring.
7 It was gone again. Our informant in San
8 Francisco indicated that phenomenon is now simply gone.
9 Go ahead, please. I don't want to spend too
10 much more time on these, just to give you an idea of the
11 scatter that occurs. Again, look at the third quarter in
12 the New Orleans area where we have a report of a 100 tablet
13 bottle of Ultram was apparently available on the streets
14 and was used in one neighborhood. We have I think 9
15 informants in the New Orleans area. None of them had any
16 evidence. Eight of the 9 could not indicate to us that
17 they had seen any tramadol use whatsoever. We finally
18 narrowed it down to our informant. We asked him, who was a
19 NIDA grantee, to go out and interview, and it appears it
20 was an isolated incident. Someone got a bottle from an
21 unknown source and these 9 or so people used it. There has
22 been nothing ongoing since.
23 But I think again a good intervention technique
24 in this case is two of the NIDA grantees voluntarily have
25 now begun to screen tramadol in the urines of all their

1 populations in the New Orleans area. This is the type of
2 cooperation we've been having with the National Institute
3 on Drug Abuse throughout this, which they actually view as
4 their mission to monitor street use.
5 Let's go to the fourth quarter. You can see
6 again New Orleans has disappeared from this thing, as has
7 California.
8 I think the other key point here, high levels
9 of abuse were simply not detected in areas that have large
10 drug-using populations: Boston, Chicago, Detroit, Los
11 Angeles, New York, Philadelphia, and south Florida. We
12 simply haven't seen any cases there. We've asked our
13 informants. You can see we have lots of key informants
14 there. We have lots of NIDA grantees there. Our reports
15 keep coming back negatively. We are told, as we contact
16 the informants, it isn't a big drug. They tried it, they
17 don't like it. It's not a very good opiate. They've got a
18 plethora of other drugs available. Why would they take
19 that one? It's simply not appearing in these particular
20 areas.
21 Can intervention strategies be developed to
22 reduce abuse and misuse of tramadol? I've actually already
23 reviewed most of these data for you. I've indicated what
24 we've done in most cases is quite frankly what we've always
25 done, is enhance the surveillance efforts because much of

1 what we saw was street use which appeared to be transient,
2 self-limiting, and dissipated by itself. The advice from
3 all the informants we got was simply let's enhance the
4 monitoring. In some cases we'll start asking direct
5 questions about tramadol, and we'll keep you posted.
6 And we've site-visited many of these areas, by
7 the way, and again I want to emphasize we had teams of
8 people flying around the country to try to characterize the
9 abuse. That was our most important strategy. Most of the
10 time with street abuse the recommendation was to simply let
11 it go because it was transient experimentation. We talked
12 to a couple of addicts who tried it who said this was a
13 lousy drug. I used it because nothing else was available
14 at that particular point.
15 But there were a number of areas -- Phoenix and
16 Atlanta, as you may have noticed on those two slides --
17 that were particularly troublesome, and there seemed to be
18 a disproportionately large number, maybe 20 percent of the
19 total cases occurring in those two cities, which was
20 somewhat unusual. We were getting a very strong message
21 from there that physicians were using this as a safe drug
22 to use in people with a drug history. Our response to that
23 was an immediate one.
24 Again, eight site visits were conducted, and in
25 particular, in both Phoenix, Atlanta, and Salt Lake City we

1 had two site visits to the areas to try to characterize the
2 nature of the abuse, what was being experienced, what was
3 the nature of the problem so we could figure out what was
4 going on.
5 I then met with the entire sales force on two
6 occasions to reinforce that they convey the appropriate
7 message to the physicians, that is, that it has low abuse
8 potential, not no abuse potential. Physicians may not
9 understand it. Because this is not scheduled, it does not
10 mean it has low abuse potential. Ortho-McNeil was
11 enormously valuable in this by actually then quizzing the
12 physicians to ensure that they had heard the appropriate
13 message and whether in fact the appropriate message was
14 being conveyed.
15 On nine occasions I actually traveled to the
16 regions where we had reports that tramadol was being used
17 as a safe, nonaddictive drug to talk to the individual
18 sales force for up to two or three hours to go through the
19 basic principles with them and reinforce the message that
20 they had to be the main source of information to
21 physicians, and if their physicians were misunderstanding
22 the message, then we had to do more educational efforts in
23 that area.
24 I think this has been very successful. If you
25 look at the next slide. Since we've instituted these,

1 particularly in the Phoenix area, the Atlanta area, we have
2 had absolutely no additional cases in the last six months
3 of any patient reporting that they were given tramadol as a
4 safe, nonaddictive drug. I think this is a fairly good
5 example where we can in fact intervene. We can in fact by
6 increasing the education.
7 Now, honestly, it is quite possible that these
8 would have spontaneously dissipated by themselves. Given
9 the transient nature of this use, it is conceivable that
10 this abuse may have dissipated by itself anyway, but the
11 committee simply wasn't willing to take that sort of risk
12 and said, no, we must go in and actively try to intervene
13 at that point.
14 What does a typical individual found to have
15 abused tramadol look like? These are the 247 cases that
16 you've seen before. In all but 2.6 percent, 97.4 percent
17 of everyone who was classified as being positive for,
18 again, DSM-IV criteria had a positive history of drug abuse
19 when we had such information available. There were only 5
20 individuals out of a total population base I guess of 16.5
21 million, but certainly of the 247, for which we could not
22 document that there was a history of substance abuse. Our
23 conclusion is it principally appears to be a problem
24 confined to people with a prior history of substance abuse.
25 Our conclusions. The experience to date

1 validates the original recommendation by this committee
2 that this drug should be nonscheduled. The rate is low as
3 predicted, and we would argue that, again, on a risk-
4 benefit analysis, a number of patients are benefiting from
5 a medication that they might not otherwise benefit from,
6 and I think this is contributing to the better treatment of
7 pain in this country. And the risk of abuse has been
8 minimized in this situation, and we believe is at
9 acceptably low rates. Any abuse case is of course a matter
10 of concern, but again, as Dr. McCormick's slide shows, we
11 have to balance these things out. Is that a risk we're
12 willing to take for the benefits of the drug?
13 The rates of abuse and dependence increased.
14 Again, I'm just repeating some, but during the first year
15 after launch to about 2 cases per 100,000. They since
16 declined to levels of less than 1 case per 100,000 for all
17 of 1997.
18 The abuse was geographically dispersed. It was
19 very transient in nature. A lot of data reviewed for you.
20 And, of course, drug abuse was a common feature
21 in most of the cases of abuse that were observed.
22 The proactive component of the independent
23 steering committee generated over 50 percent of the
24 abuse/dependence cases.
25 And finally, intervention strategies we think

1 can be implemented to reduce abuse as it occurs.

2 I do want to spend a moment now at the end of

3 this just to illustrate because I think it's very confusing

4 when you're going to hear a presentation this afternoon

5 which suggests that the number of cases coming from the

6 committee is much lower than we had reported in our report,

7 and I think the explanation is on the next slide.

8 Now, remember who our informants are. They're

9 drug abuse experts. These are people who know DSM-IV.

10 They classify and report to me cases of positive for abuse.

11 If you look at abuse/dependence now, only 47

12 percent of those come from Ortho-McNeil, and again the

13 number has recently flipped over. 52.2 percent of those

14 are coming from the committee. We are generating more than

15 twice the cases of abuse and dependence and it's simply a

16 feature of our system. We have drug abuse experts being

17 asked to report to us what is abuse or dependence of

18 tramadol. They're not going to report some of these other

19 categories. They simply will not report them.

20 I think Dr. Alderfer may be referring to these

21 numbers out here in terms of what the percent contribution

22 of the committee is, and that makes all the sense in the

23 world. As the degree of certainty drops, whether in fact

24 it's abuse or dependence, the contribution from the

25 committee correspondingly drops. Of course, withdrawal is

1 not reported by our informant network because they
2 recognize that withdrawal, in the absence of other DSM-IV
3 criteria, particularly drug-seeking behavior, is simply not
4 abuse. So, 93 percent of those have come from Ortho-
5 McNeil, and as you can see, that's the vast majority of the
6 cases.
7 We believe this explains the comment being made
8 that the independent steering committee collected
9 relatively few, and I think the implication of that comment
10 is that enough abuse has been detected by normal patterns
11 to, I guess, potentially indicate that the steering
12 committee's contribution was not that valuable. We suggest
13 to you, you must focus on this column, and this is
14 extremely important.
15 What is also important is again this number is
16 the only thing that would be available to us today using
17 spontaneous reports without the committee influence. So,
18 we would be grossly underestimating what the level of abuse
19 actually is in this country.
20 Our recommendation at this point is that
21 tramadol should continue to be marketed as a noncontrolled
22 drug since the abuse rate has been low. It is not
23 widespread. It has been quite transient.
24 We believe, though, that surveillance efforts
25 should continue to provide an early warning of any sudden

1 emergence of tramadol abuse. We haven't seen much. We saw
2 some experimentation which has dropped off now. I have no
3 idea what might occur in the future. Again, recall this is
4 the first systematic study that has ever been carried out
5 looking at the dynamics of abuse. We have no clue whether
6 we might see another outbreak of experimentation at any
7 given point. The committee should remain in place or some
8 form of surveillance should remain in place to guard
9 against that.
10 And then the final point. Should abuse emerge,
11 proactive intervention strategies can and we believe should
12 be developed.
13 I want to move along to one more set or slides,
14 and I think this will be touched upon by other speakers but
15 I think it bears me mentioning it again today. You will
16 hear some of it this afternoon. Dr. Alderfer has covered
17 this quite well, the limitations in spontaneous reports. I
18 think the danger of including withdrawal -- I want to show
19 you a slide which I think illustrates that.
20 If you look at the total cumulative positive,
21 alleged, and withdrawal cases -- I'm looking at the
22 cumulative number. I'm just taking cumulative numbers, and
23 I'm sure you'll see this number this afternoon. There are
24 around 650 cases total that include withdrawal, alleged,
25 positive. Now, this is both the committee and spontaneous

1 reports. If you take away withdrawal, just take out
2 withdrawal cases now, that number of course drops by nearly
3 50 percent. If you further take out and only look at
4 spontaneous reports, the number drops all the way own to
5 there. I think this is really a dramatic demonstration of
6 the contribution of the steering committee and, in
7 addition, points out I think how the data are skewed by the
8 inclusion of withdrawal as abuse because these cases again
9 do not satisfy the criteria for abuse.
10 It becomes important when you start to try to
11 make comparisons between this number, which is grossly
12 unfair because this includes -- not only does it include
13 withdrawal, but it includes the committee-generated
14 reports. When you're trying to compare it to other drugs
15 for which only spontaneous reports exist, it is an
16 extremely unfair comparison which we don't believe again is
17 in the interest of the public health.
18 I do want to mention DAWN. You'll hear a bit
19 about DAWN this afternoon. Again, this data is relatively
20 new to us, and I think you're all well aware of the
21 limitations of DAWN. There was a special run that DAWN
22 made to get these data. I believe the FDA requested that
23 run, and we just got the data.
24 Again, it's difficult for us to make a lot of
25 sense with these data because in the DAWN system, as you're

1 all aware, there are certain classifications, and if
2 tramadol is one of up to four drugs, it will be included in
3 the analysis. It doesn't necessarily mean that tramadol
4 was the drug that was in question or tramadol alone. Those
5 data are very difficult to tease out and to get much
6 information from.
7 The best way to look at it then is just look at
8 relative rates again of DAWN mentions, and let me show you
9 the next two slides real quickly.
10 This is just taking 1994 data. Of course,
11 tramadol is for 1996 because it's the only data that we've
12 got available. We just simply took a number of drugs that
13 are in the DAWN system. Now, again, we had these, so we
14 could look them up. We don't have data for 1996. It
15 included a bunch of drugs, obviously many of which are not
16 scheduled, and just looked at the number of emergency room
17 mentions per prescriptions to calculate a rate. Tramadol
18 is down at 13, equivalent to erythromycin. This is not a
19 big problem in the DAWN system.
20 This is an actual analysis of the data that the
21 FDA requested a run on codeine, chloral hydrate,
22 amitriptyline, hydrocodone, propoxyphene, Prozac, and then
23 tramadol. Again, the rate for tramadol with these
24 projection of prescriptions is only 13 compared to, you can
25 see, much larger numbers. So, without doing any more

1 detailed analysis, we would suggest to you the DAWN data
2 actually end up supporting our conclusions that this is not
3 a big problem. This has not become an issue of importance.
4 That simply adds some confirmatory evidence,
5 although I certainly don't want to hang my hat on the DAWN
6 data. I think there are many flaws and problems with the
7 data. But I think it just generally does support our
8 conclusion.
9 Once again, in 1994 you made I think a
10 courageous decision to not schedule tramadol based upon
11 some estimates of what abuse was likely to be. We now have
12 collected I think systematic data that validate that that
13 was the appropriate decision at that time, and based upon
14 an analysis of the data, it would be the independent
15 steering committee's conclusion there is simply no basis to
16 change the controlled status at this point.
17 One further point. Curt Wright is gone. I
18 think Curt was very much involved in one of the initial
19 discussions with this. We viewed this as a potential model
20 as an alternative to scheduling. What is the purpose of
21 scheduling? Protection of public health.
22 If in fact we could come up with an aggressive
23 post-marketing surveillance program that was overseen by an
24 independent steering committee that was not scheduled -- we
25 all acknowledge the fact scheduling has a chilling effect

1 on prescribing practices. If we could in fact have a drug
2 that was used for the treatment of pain and at the same
3 time implement an aggressive post-marketing surveillance
4 program with intervention techniques, that would actually
5 be far more preferable to a simple scheduling decision.
6 It's our conclusion now, only after three
7 years, at this time that indeed we have not only ratified
8 and validated the decision made in 1994, but that we have
9 indeed suggested that this may well be an excellent model
10 for future drug analysis of a similar nature.
11 I think I've taken my 40 minutes. I'll stop.
12 DR. STRAIN: Thank you, Dr. Cicero.
13 At this point we will take a 15-minute break
14 and reconvene here at 10:25.
15 (Recess.)
16 DR. STRAIN: Next we'll be hearing from Dr.
17 Savage on clinical issues relating to drug abuse, pain
18 treatment, and scheduling.
19 DR. SAVAGE: Thank you very much. I very much
20 appreciate the opportunity to participate in these
21 discussions regarding the scheduling status of tramadol. I
22 believe that these discussions really have implications far
23 beyond this particular drug, that they are very important
24 with respect to this particular drug.
25 I'll be speaking to you from the perspective of

1 a clinician and an educator with experience in both the
2 fields of pain medicine and addiction medicine. I've had
3 the opportunity to be the director of an interdisciplinary
4 pain clinic, an outpatient pain clinic, in an academic
5 center focused primarily on the treatment of chronic pain
6 problems, and also the opportunity to be medical director
7 of an inpatient drug and alcohol treatment center for many
8 years at both sites. So, I come to these issues with a
9 real dual perspective.
10 I have the privilege of chairing the Committee
11 on Pain for the American Society of Addiction Medicine and
12 sitting, on the other hand, on the Committee on Chemical
13 Dependency for the American Academy of Pain Medicine.
14 My interest is at the interface between pain
15 and addiction and particularly in how we might use
16 analgesic medications most effectively to relieve pain and
17 suffering in our patients while at the same time avoiding
18 potential complications of abuse and addiction.
19 It's really these public health goals that I
20 think you were addressing in these discussions regarding
21 whether tramadol should become a scheduled medication or
22 remain unscheduled as it is now. On the one hand, the
23 public health goals are to provide effective and readily
24 available analgesics to relieve pain, to reduce the very
25 real suffering that comes from living with chronic pain,

1 which can sometimes end in catastrophe for patients, even
2 in suicide when pain is untreated.
3 On the other hand, there is a responsibility to
4 protect the public from widespread diversion of highly
5 abusable drugs and to protect patients from the sequelae of
6 abuse and the development of the disease of addiction and
7 the morbidity and mortality associated with those problems.
8 I think as new analgesic drugs are introduced
9 into the marketplace, this is going to become a more
10 complicated process. It's no longer as simple as saying,
11 well, this drug has mu opioid activity, it needs to be
12 scheduled. There are drugs in the pipeline now that have
13 combined mu receptor activity, other opioid receptor
14 activity which interact with a variety of other
15 neurochemical pathways in the body. We're beginning to
16 accumulate evidence that there may be subtypes of mu
17 receptors, and we note that all mu agonists don't behave
18 similarly. So, as we approach these questions of
19 scheduling drugs and protecting the public, we need to
20 really do a very careful risk-benefit analysis of the role
21 of the drug as it emerges in society.
22 We know that pain is undertreated in our
23 country and in fact throughout the world. There are few
24 who would argue this. These are just a few data looking at
25 postoperative pain from the Acute Pain Guidelines put out

1 by the United States Department of Health and Human
2 Services in 1992, quoting statistics that suggested that
3 greater than 50 percent of individuals undergoing surgery
4 in this country continue to suffer from significant pain
5 postoperatively despite the fact that we have adequate
6 tools to amply relieve pain postoperatively.
7 Similarly, from the Cancer Pain Guidelines,
8 also by the United States Department of Health and Human
9 Services, statistics suggest that 40 to 50 percent of
10 patients with cancer pain experience during the course of
11 their illness moderate to severe pain and 25 to 30 percent
12 very severe pain despite the fact that we have tools to
13 manage this.
14 It's a bit harder to get exact statistics for
15 chronic non-cancer pain for a variety of reasons, but
16 estimates are routinely in the billions of dollars when we
17 add up the health care costs of meeting the medical needs
18 of individuals with chronic non-cancer related pain and in
19 lost productivity, loss of workers from the work force, the
20 impact in domestic settings, and other costs that accrue in
21 the course of treating chronic non-cancer pain.
22 If we ask the reasons that pain is
23 undertreated, there are certainly many. Western medicine
24 tends to focus primarily on the cure of disease and on the
25 relief of acute problems, rather than on palliative care

1 and on the relief of symptoms and pain and suffering. We
2 have very little education in our medical schools during
3 post-graduate training programs on pain management and
4 techniques of pain management. These are improving but
5 there are still problems.
6 However, often cited as most problematic are
7 confusions regarding the definitions of addiction and abuse
8 versus physical dependency and the impact of regulation of
9 available drugs on doctors' prescribing habits.
10 Now, few would argue that regulation of
11 medications impacts the doctor's readiness to prescribe
12 medications. Dr. Weintraub's study that was published in
13 1991, looking at the impact of triplicate prescribing of
14 benzodiazepines in New York State, found that diazepam
15 prescriptions reduced radically while at the same time less
16 specific, less effective, and possibly more toxic
17 medications, such as meprobamate, chloral hydrate, increase
18 commensurately quite significantly, suggesting that doctors
19 are willing, when regulatory scrutiny is increased and the
20 hassles of such regulation impact their practices, to
21 substitute less effective drugs that may have more toxic
22 consequences for their patients.
23 Dr. Edgar Adams has recently completed two
24 surveys which are prepared now to be submitted for
25 publication, one in 1993 looking at 270 some patients, and

1 one in 1997 surveying 600 physicians related to doctors'
2 understandings and attitudes related to the scheduling of
3 medications. Among many other findings, he found that 54
4 percent of doctors acknowledge that they would readily
5 choose a lesser regulated drug or an unscheduled drug when
6 treating chronic pain than choosing a scheduled drug, all
7 other factors being equal.
8 Similarly, Dr. Portenoy, who is a noted pain
9 specialist, reported the results of a New York State survey
10 which was completed last year. I do not believe this has
11 been published yet, but his findings were essentially that
12 many physicians acknowledged that they occasionally or
13 frequently substitute unscheduled medications for scheduled
14 medications, even when aware that a scheduled medication
15 may be more efficacious for their patients.
16 From these studies and many, many others that
17 are in the literature, it is clear that the scheduling
18 decisions regarding tramadol may well impact its
19 availability to patients for treating pain.
20 So, in making these decisions, we really need
21 to weigh the value of the medication against the abuse and
22 addiction potential of the medication. Physical dependency
23 and withdrawal cannot be a consideration in this. From a
24 clinical point of view, it is inappropriate to make that a
25 consideration.

1 You've already heard a lot about this. At the
2 risk of boring you with more on that subject, I do just
3 want to highlight it a bit because I think it's so
4 important and there is so much confusion in our culture
5 among patients, among physicians, among regulators about
6 these issues.
7 As we're aware, abuse and addiction refer to
8 pathologic behavioral phenomena which may reflect an
9 underlying neurobiological disorder induced by repeated use
10 of drugs, but these are pathologic behavior phenomena.
11 Physical dependence, withdrawal, and tolerance, on the
12 other hand, refer to non-pathologic and expected
13 physiologic sequelae of prolonged drug use.
14 I should mention that the word "dependence" has
15 been used in many of these deliberations to mean addiction
16 and not to mean physical dependence, the physiologic
17 phenomenon. I find that a little confusing so I prefer to
18 use the word "addiction," but I know that DSM-IV uses
19 substance dependence as the equivalent of addiction. So,
20 we need to distinguish between those two uses of the word
21 "dependence."
22 So, physical dependence we know occurs in many
23 settings. It's not just a factor of opioids. There are
24 many, many other drugs. Beta blockers, tricyclics,
25 prednisone, some antihypertensives all have well defined

1 withdrawal sequelae if they are stopped abruptly or in some
2 cases if they are radically reduced without a taper. We
3 note these symptoms of withdrawal, note that the individual
4 has neuro-adaptation or endocrine adaptation to the drugs,
5 but we don't say these individuals are addicted to their
6 prednisone.
7 Similarly with mu opioids, we see pain patients
8 who use these drugs for months at relatively high doses and
9 even years in some cases and are tapered from their
10 medications. They will develop a withdrawal if the
11 medications are abruptly stopped, but they're not addicted
12 to their medications. They have a physical dependence.
13 We also know that addiction can occur without
14 physical dependence. We have individuals who have intense
15 craving and biologic addiction to, for example, cocaine or
16 who use a binge pattern of alcoholism and may go for weeks
17 or months without using the drug, then binge because of
18 their addiction and withdrawal without the classic
19 withdrawal phenomenon.
20 Similarly, we know that there are analgesic
21 medications such as the experimental drug dihydro-etorphine
22 which have virtually no physical dependence but are highly
23 abusable and well liked by addicts.
24 So, these are emerging as truly independent
25 phenomena. And on a neurobiologic level, as we're

1 beginning to understand the mechanisms of addiction and the
2 mechanisms of physical dependence, a picture is emerging of
3 these as separate neurobiologic phenomena with addiction
4 and abuse and craving phenomena that occur related to
5 dopamine changes in the limbic reward systems and physical
6 dependency being a more widespread issue dealing with
7 receptors and second messenger systems in the periphery, in
8 the spinal cord, as well as in the brain.
9 These are not radical or controversial ideas.
10 They are widely accepted. There is great consensus among
11 clinicians. All the agencies that I've listed here have in
12 official documents made statements documenting the need to
13 separate physical dependency from addiction and abuse. The
14 Cancer Pain Guidelines of the U.S. Department of Health and
15 Human Services, the American Pain Society, the American
16 Academy of Pain Medicine, the American Society of Addiction
17 Medicine all have public policy statements making this
18 distinction. So, it's both in the pain community and the
19 addiction community that we see these views.
20 I had the opportunity to review draft
21 guidelines of the Federation of State Medical Boards, which
22 has not yet been ratified but is expected to be in the next
23 few months, on opioid prescribing to be disseminated to
24 state boards for adoption or modification to their states'
25 needs. These too made the separation between the physical

1 dependence and addiction withdrawal.

2 As an aside, talking with Dr. Edgar Adams

3 recently, he pointed out that were there not this problem

4 of regulation and doctors under-prescribing because of

5 regulations, the Federation of State Medical Boards would

6 not now be in the process of adopting guidelines to provide

7 security for physicians who use opioids for the treatment

8 of pain.

9 One final comment on physical dependency which

10 I think is real illustrative. This is really a cartoon

11 mockup of a case that has been presented in pain medicine

12 literature and at conferences, but it's a typical case

13 that's seen frequently, almost daily, in pain clinics.

14 What we have on the y axis is milligrams of morphine

15 consumed a day, and the x axis, passage of time without

16 demarcations, but this is weeks and months passing on here.

17 This is an older woman with metastatic

18 carcinoma who developed pain associated with her disease,

19 gradually increased her use of morphine over weeks and over

20 months, plateaued as her disease was stable. She then

21 developed spinal metastases with very painful bony

22 invasion, and markedly over weeks increased her use of

23 morphine up to over 700 milligrams a day. A cordotomy, a

24 neurosurgical procedure which can be definitive in

25 relieving certain pain syndromes, was then undertaken.

1 Despite warnings from her doctor not to stop
2 the medications because of the development of acute
3 withdrawal, she felt she didn't want to be on the morphine,
4 she didn't need the morphine. She was pleased to be
5 without pain, without the drug and she stopped the
6 morphine. As her blood levels fell, she went into acute
7 withdrawal within 36 hours and developed all the classic
8 signs of withdrawal. She did not wish to restart her
9 medications, but agreed to start on a low dose and was
10 finally tapered off the medications.
11 This happens all the time. Pain patients
12 discontinue their medications. They go into withdrawal.
13 They have physical dependency. They do not return to use.
14 They are not addicted.
15 So, looking at what are reasonable issues to
16 consider, the important issues to consider, the abuse
17 potential of tramadol. I think Dr. Cicero's group and
18 their work has really elegantly demonstrated the low abuse
19 potential of tramadol with less than 1 case in 100,000
20 exposures over the past year using very conservative means
21 of measurement identified. He has noted migratory bursts
22 of experimentation with no further experimentation.
23 And with all due respect for the intervention
24 component, I think the pattern of extinguishing of
25 experimentation with those modest interventions really

1 suggests that they would extinguish of their own accord
2 because it would be quite likely that they would accumulate
3 over time again in those areas.
4 What we expect to see in an abusable drug is
5 experimental versus experimentation and then a gradual
6 increase up to a plateau when the drug-abusing population
7 is saturated in terms of that use of the drug. We don't
8 expect to see use extinguished in geographical areas.
9 Finally, the negligible activity on the
10 Internet in this day and age is extremely telling. Addicts
11 share information about drugs. Abusers share information
12 about good recreational drugs. The fact that we don't see
13 discussions on the Internet is really telling about the
14 very low abuse potential of this drug.
15 And that is not to say that there is no abuse
16 potential. There are isolated case reports of individuals
17 who do abuse only tramadol. These are exceptionally rare,
18 but they do occur. Hence, the designation of low abuse
19 potential, but one has to wonder if those are phenomena
20 more of host factors than of drug factors alone, as is
21 always the case in addictions.
22 Finally, the clinical impression of colleagues,
23 many whom I've talked to over months and years regarding
24 this drug, both in pain circles and in addiction medicine
25 circles, is addicts simply don't like tramadol.

1 I had the opportunity a couple of months ago at
2 a conference on pain and chemical dependency that was
3 attended by over 400 clinicians in the field of pain
4 medicine and in the field of addiction medicine to be asked
5 that question. Well, what do you think about tramadol?
6 What's the abuse potential of tramadol? I said very
7 simply, it's my impression that addicts don't like tramadol
8 from my clinical work and talking with colleagues. And
9 there were nods all around the room. There was no one who
10 raised their hand to tell stories or give their theories of
11 addicts or abuse of tramadol.
12 So, we have to look at the value. With a low
13 abuse potential, we have to weigh this against the value of
14 tramadol as a medication. I believe that it really fills
15 an unmet need in pain treatment. It's a moderately potent
16 analgesic appropriate for moderate to moderately severe
17 pain, particularly efficacious in the treatment of chronic
18 pain.
19 It has less toxicity certainly in terms of GI
20 side effects at therapeutic doses than do the nonsteroidal
21 anti-inflammatories, and so for many patients may be a
22 preferred drug.
23 It certainly has a lower abuse potential than
24 pure mu agonist opioids, and we'd have to speculate on the
25 reasons for that and I think many of us could if there is

1 interest in that. But clearly that has been demonstrated.
2 And because it does not have a linear effect on
3 CO2 retention and respiratory depression with use in high
4 doses, it has less potential for significant and life-
5 threatening morbidity when it is abused than pure mu
6 opioids do, even ones that are scheduled as weak opioids,
7 which we all know are simply a dose-related phenomenon.
8 Codeine in high doses can have the same effect as morphine
9 when the doses are titrated appropriately.
10 Finally, it's current unscheduled status
11 certainly facilitates its use in its appropriate role I
12 believe.
13 So, in summary, we recognize that pain is
14 undertreated. We recognize the need for unscheduled
15 effective analgesics. Again, as new drugs come down the
16 pipeline, we really have to look at the data on abuse
17 rather than just looking at the pharmacology of the drug
18 because there will be more and more complex drugs providing
19 analgesia, some of which will have mu activity which may
20 have low or no abuse potential.
21 The risks of use of tramadol are low. There's
22 a low abuse and addiction potential which we've seen.
23 There's a low risk of serious respiratory morbidity
24 associated with abuse, and we have an elegant and effective
25 screening system in place to monitor abuse, should it

1 occur. I do agree that this should continue for the time
2 being, but that will effectively detect changes in patterns
3 that might be a threat to the public health.
4 Physical dependence is not relevant.
5 I believe that public health goals really are
6 best met by tramadol remaining unscheduled. If this drug
7 is scheduled, we would expect to see decreased availability
8 of this agent. We would likely -- not certainly, but
9 likely -- see the substitution of less effective
10 medications and possibly more toxic medications for some of
11 our patients.
12 And then the final comment is not based on data
13 but on kind of a common wisdom among addictionists or
14 individuals working with people who abuse drugs and become
15 addicted to drugs, and that is, for at least a short period
16 of time, scheduling will be a flag that will attract
17 individuals to abuse the medication. I don't expect that
18 that abuse would be sustained because the drug is not a
19 good advertisement for itself in terms of its satisfaction
20 of abusers' recreational needs, but I do think that it
21 would be a flag and there would be a few episodes of abuse
22 increase.
23 That concludes my comments.
24 DR. STRAIN: Thank you, Dr. Savage.
25 Next we'll hear from Dr. Jones on the

1 epidemiology of tramadol abuse.

2 DR. JONES: Thank you, Dr. Strain, ladies and

3 gentlemen.

4 As one who has worked in the area of post-

5 marketing surveillance for the last 20 years, I was asked

6 by the sponsor to make some remarks that specifically

7 relate to the analysis of the spontaneous reports and,

8 secondly, the perspective of the overall post-marketing

9 surveillance program.

10 I'm going to be just briefly alluding to the

11 place of post-marketing surveillance in this area and

12 speaking about the analysis of spontaneous reports and then

13 going back to considering the components of an overall

14 post-marketing surveillance strategy and just to comment

15 briefly on the independent steering committee.

16 I will just mention in passing that this is the

17 one area of post-marketing surveillance where the data

18 derived in post-marketing surveillance is almost all -- the

19 only data that one can derive other than the trials

20 described by Dr. Jasinski because of the particular nature

21 of them, the structured setting, the controls, and most

22 notably the kinds of patients that are participating in the

23 trials who do not usually match the kinds of people who

24 would be potentially abusing it. So, therefore, we must

25 rely entirely upon the methodology in this period of time.

1 Now, in considering what an overall program
2 would consist of, typically it is composed of spontaneous
3 reports and structured studies. In this particular case in
4 abuse, we also have focused active surveillance, and the
5 advantage of this is that if it's positive, it provides a
6 signal; if it's negative, it suggests a lower potential
7 likelihood.
8 What I'd like to do is to spend just a few
9 moments looking at the unit of analysis of the signaling
10 mechanism and consider what the issues are from the event,
11 which is really the unit, and its likelihood of being
12 reported. Essentially we're speaking about a variety of
13 events that might occur which in fact may, depending upon
14 the nature of the event, be related to more than one drug
15 or other underlying diseases, environmental factors, et
16 cetera.
17 Now, the first condition is that that event has
18 to be detected. There are a number of factors which may
19 determine whether or not it is detected. In the case of
20 the kinds of events we're speaking about here, it is
21 dependent upon the setting in which it's observed. It's
22 also dependent upon the kind of physician. For example, a
23 physician in an abuse clinic would be much more likely to
24 detect an event related to this than, say, an
25 ophthalmologist or a dermatologist. So, the events from

1 those other sites might not be even detected or recorded.
2 So, therefore, in the given universe of events that might
3 be detected, a certain proportion are not detected, a
4 certain proportion are.
5 At the next step, we have the attribution to a
6 particular cause, and it may be to one drug or another drug
7 depending upon certain biases of the observer or certain
8 knowledge that the person may have at any particular time,
9 certain biases of the patient who has the event.
10 Therefore, in some cases events will not be attributed to
11 the drug in question, some will, but not the whole
12 universe, and there is considerable variation around this
13 attribution and detection step.
14 Finally, the question is, how many are
15 reported? As I think everyone generally appreciates, with
16 respect to the spontaneous reporting system, only a
17 proportion of the events in fact are reported. A lot of
18 this relates to structure of the reporting system and the
19 stimulus for reporting. For example, in the stimulated
20 reporting system, there's more likelihood of reporting
21 because of the administrative steps that have been taken to
22 promote that reporting. In the natural circumstances, a
23 high proportion of physicians do not know anything about
24 the reporting mechanism. So, there is sometimes a
25 reporting system.

1 However, the most important point about all
2 three of these steps is that they vary from drug to drug
3 and from time to time. We have seen over the past 20
4 years, a tremendous increase in the number of reports to
5 the spontaneous reporting system at the Food and Drug
6 Administration starting in 1978 from about 12,000 to well
7 over 100,000 per year. So, this system has changed
8 considerably and it makes it difficult to compare new drugs
9 with old drugs.
10 Just to repeat a bit, there are a lot of biases
11 that affect the system at a lot of levels, and they relate
12 not only to information biases -- and that includes both
13 physician and patient which drive the system -- but also
14 literature and media biases which change over time.
15 The disease severity or lack thereof is going
16 to affect the likelihood of detection and attribution and
17 certainly the timing of the disease relative to initiation
18 of the drug.
19 As I mentioned, there are a number of
20 administrative factors, and the reporting to FDA is
21 continually increasing. Consequently, the numbers of
22 reports that are in the system, the absolute numbers,
23 cannot be a reliable estimate of the rate of actual events
24 occurring because there are biases occurring at all of
25 these levels. As a corollary to that, the comparison of

1 reports on different drugs, even those that are very
2 similar and sometimes look rather similar in an analysis
3 report, cannot be reliable for risk assessment and a
4 quantitative assessment of either the numbers of the report
5 or secondarily because of differences in perception,
6 detection, and the actual pharmacologic characteristics of
7 the drug, the percentage or proportion of events seen from
8 one drug to another. We've actually recently submitted or
9 actually had published a report describing this for
10 nonsteroidal anti-inflammatory drugs in the October 13th
11 Archives of Internal Medicine.
12 In addition to being nonquantitative, I think
13 all of the speakers before me have emphasized the fact that
14 we probably should not be counting the term "withdrawal" as
15 a component of abuse. Withdrawal is associated with a
16 number of other drugs that would never be considered for
17 scheduling such as beta blockers and clonidine.
18 Finally, the issue of causality I do believe is
19 one to be considered. In a number of the cases that we're
20 speaking about, there are other possible causes and just
21 because a drug is associated temporally with an event does
22 not necessarily mean that it's causally related to it. And
23 it's important to be somewhat cautious about that.
24 Therefore, the numbers of these reports cannot be used in a
25 specific fashion.

1 Now, in considering the epidemiology of abuse
2 and comparing it with the traditional adverse effect of
3 abuse, there are some differences. Obviously, in the case
4 of pharmacologic effect, you basically have the
5 pharmacology of the drug and the clinical risk factors, but
6 in the case of abuse, you have not only pharmacology and
7 the clinical risk factors, but also the social/behavioral
8 factors specifically that are challenging those, the
9 geographic clustering, as we heard about, the social role,
10 and a special susceptible population who may not be part of
11 the traditional medical care system.
12 One advantage for the stimulated surveillance
13 that was described in the independent steering committee
14 system is the fact that it does provide the greatest
15 likelihood of getting cases and getting them so one can
16 describe them and understand them. There's a precedent for
17 this in the case of the toxic epidermal necrolysis in
18 Germany where basically they were able to get almost all
19 cases in that country, and obviously in looking primarily
20 at the sites where things are occurring, such as the
21 tertiary referral hospital.
22 In practice, the stimulated surveillance, going
23 to the site of likely occurrence of event, is not strictly
24 quantitative. That is, there are some cases that may be
25 missed, but it has tremendous advantage, when one is

1 looking from a public health standpoint, to know that if
2 the event is occurring, it is likely to be detected and
3 detected earlier. That is, you know much earlier than you
4 would from a completely passive system.
5 Secondly, it's going to be seen more often, and
6 the opportunity to describe this and understand the risk
7 factors for this, as Dr. Cicero described, is a tremendous
8 advantage in being able to understand the nature of the
9 problem and understanding any interventions that might be
10 utilized.
11 But there is no single ideal method for
12 understanding and quantifying drug abuse, as Dr. McCormick
13 pointed out, and in the next slide, there is a sketch of
14 sort of the overall comprehensive system of looking, if you
15 will, at the elephant which is made up of both
16 nonquantitative or qualitative methods for understanding
17 the problem. Of course, the major component of this are
18 the spontaneous reports which are very valuable for
19 understanding the dimensions and characteristics of the
20 problem, supplemented from signals from sentinel groups who
21 are really looking for this.
22 But it really ultimately calls for the need to
23 look at population based data which can test these
24 hypotheses by understanding the actual rate in the
25 population as, for example, in the screening defined

1 population of physicians, in a cohort study, or large
2 clinical trial, and in fact, in the national system of the
3 Drug Abuse Warning Network, which does have the whole
4 United States roughly or most of the major -- SAMSHA is
5 their catchment area.
6 It is only with the combination of these, both
7 the nonquantitative and the structured studies, that you
8 really get a good understanding of the drug use in actual
9 use. This cannot be done immediately. This is really
10 being accrued over time as we go on and improve our
11 understanding.
12 I think I wanted to just comment about the
13 independent steering committee. As a student of post-
14 marketing surveillance for these many years, I think that
15 this particular effort represents a particular robust,
16 multidimensional effort that greatly increases the
17 likelihood of having a good understanding of the
18 surveillance of possible abuse of a drug, specifically for
19 early detection and characterization of the type of abuse
20 that might be occurring, and included in that is the
21 physician surveillance, and secondly, an understanding of
22 the multiple dimensions of this, the qualitative nature of
23 abuse when it does occur, and has been observed and
24 described, as we've heard before.
25 But more importantly, the other components of

1 this, which are still ongoing, allow a fair comparison, a
2 balanced comparison in a structured trial where you really
3 do have a very defined denominator and numerator. That
4 will be I think a better way to look at comparisons.
5 So, finally, in the last slide, I want to make
6 a point that the spontaneous reports, although very
7 valuable for understanding and signaling a problem, are the
8 weakest quantitative data source. They really aren't
9 quantitative. The data used has a danger because they're
10 incompletely described, describing both abuse and non-
11 abuse. In fact, there are, as we heard about, better
12 population-based data available.
13 The current structured surveillance, which
14 includes the independent steering committee as well as the
15 Drug Abuse Warning Network, provides a much better and more
16 balanced basis for understanding the potential and rate of
17 abuse in a population-based way and a basis for looking at
18 comparison drugs in a contemporary fashion, which I think
19 would be more balanced.
20 Thank you very much, and I'll turn this back
21 over to Dr. Burton.
22 DR. STRAIN: Thank you, Dr. Jones.
23 I think we'll be hearing next from Dr. Burton.
24 DR. BURTON: As I mentioned in my introduction,
25 Dr. Portenoy is unable to be with us today but, if I could

1 have the next slide, his written submission covered these
2 four areas. Dr. Portenoy comes from a clinical
3 perspective, indeed discussed in his written submission
4 these four areas.
5 The points he makes in his paper were echoed
6 really by Dr. Cicero in his presentation, and might I
7 suggest that Dr. Savage has actually given his presentation
8 for him from the clinical perspective because many of the
9 points she mentioned are echoed in Dr. Portenoy's
10 submission.
11 I am not going to make any more comments about
12 that written submission, but once again, I beg you to read
13 it and consider his points from the clinician's
14 perspective.
15 I'd like to conclude. I hope we're virtually
16 on time. And I'm going to make these brief.
17 I'd like now to bring the committee back to the
18 questions before you and perhaps speak to these questions.
19 Your first question. I'd like to remind the
20 committee once again that in 1994 you predicted that there
21 would be a low rate of abuse of tramadol in the U.S.
22 marketplace. Indeed, the guesstimate of 2 in 100,000 users
23 has been borne out by the independent steering committee's
24 findings to date. The pharmacological profile of the drug
25 provides a rationale to support these findings. We would

1 suggest that the Drug Abuse Advisory Committee made the
2 right decision in 1994 and it's perhaps still the right
3 decision in 1998.
4 Your second question. Ultram we believe has a
5 novel mechanism of action as an analgesic. Dr. Burks and
6 his committee have brought you up to date on this aspect.
7 Dr. Jasinski has described activity at higher
8 than normal doses and in populations who are very much
9 allied to this whole area we are discussing.
10 Dr. Cicero's independent steering committee has
11 defined and delineated a powerful methodology that has
12 picked up possible outbreaks of abuse, and to quote Dr.
13 Cicero, the pattern of abuse is not sustained and
14 persistent. It is more one of experimentation.
15 I'd like to provide another quote from Dr.
16 Savage's talk. She stated that addicts don't like
17 tramadol. Now, these quotations, for what they are, come
18 from clinicians actively involved in this field of
19 treatment of chronic pain.
20 Passing on to the spontaneous reports that
21 we've been hearing about, we have a qualitative aspect to
22 these spontaneous reports. On the one hand, we have those
23 variously described, drug abuse, withdrawal symptom, drug
24 dependency, and this subject was covered by Dr. Cicero and
25 Dr. Savage and touched on by Dr. Jones. The whole question

1 surrounding what is physical dependence resulting in
2 withdrawal syndrome versus psychological dependence
3 resulting in pathological drug-seeking behavior is a very
4 difficult question to address and indeed provide clear
5 answers to.
6 The term "discontinuation," indeed, has
7 recently been described in the literature in relation to
8 the symptoms and signs experienced by patients when they
9 stopped taking antidepressants. This seems to have been a
10 sensible effort by, in fact, another regulatory agency to
11 help in the review of such reports to better understand and
12 tease out benefit-risk in patients.
13 With spontaneous reports, we have a
14 quantitative aspect that Dr. Jones has touched on. She, I
15 believe, examined these factors in great detail, pointing
16 out the inherent weaknesses found in such systems, and her
17 message I believe is a counsel of caution in the use of
18 these data.
19 Still in relation to question 2, the
20 pharmacology of Ultram shares some features with other
21 drugs that are scheduled, especially when they investigated
22 at very high doses in man. But it is more complex than it
23 first may appear. The characteristics and properties are
24 unique to the drug. They are very different from pure mu
25 opioid receptor agonists, and as we've seen from the ISC,

1 they are associated with a low degree of abuse in the
2 community. We believe these observations set Ultram,
3 tramadol, very much apart from opioid scheduled drugs.
4 This is your third question, a difficult one,
5 but one I'm sure there's going to be much discussion.
6 The independent steering committee has
7 demonstrated its study to be sensitive, prospective, and
8 able to respond to any issues of abuse that may arise
9 throughout the U.S. Surely this methodology provides a
10 better assessment of risk than any other facility that we
11 have available to us. The beauty of this system is that it
12 performs in real time. We await your thoughts and
13 responses and your questions surrounding this system and
14 your thoughts and responses in relationship to this
15 question with interest.
16 I'd like to state that as a sponsor we have
17 always recognized that there would be some cases of abuse,
18 albeit of very low incidence. We believe that the data
19 gathered together so far supports that position.
20 Finally, scheduling does not change a drug's
21 behavior or pharmacology. The drug will always continue to
22 act as it has always acted. However, scheduling does
23 change a prescriber's behavior. He or she may no longer
24 act as they have always acted. And I'd like to quote from
25 one of our advisors at a recent meeting, that scheduling is

1 not a victimless option. We must always remember that at
2 the end of the day, we have to treat patients with painful,
3 long-term conditions.
4 Thank you.
5 DR. STRAIN: Thank you, Dr. Burton.
6 I would now like to remind the committee that
7 we would normally have a break, but we're not going to take
8 another break. We're going to press on and I would like to
9 go on to the open public hearing. So, the committee should
10 shift gears. This is not a part of the presentation of the
11 sponsor that we'll be hearing. And we do have one person
12 who has registered for the open public hearing, Dr. Warren
13 Katz from Philadelphia.
14 DR. KATZ: Good morning. My name is Dr. Warren
15 Katz. I am Chief of Rheumatology at the Presbyterian
16 Medical Center which is part of the University of
17 Pennsylvania Health System in Philadelphia, and there I am
18 Professor of Medicine at the University of Pennsylvania
19 School of Medicine.
20 I am a board certified rheumatologist and have
21 been in the practice of rheumatology, limiting my exposure
22 to patients to musculoskeletal diseases for some 25 years.
23 As part of my practice, I have had a special
24 interest in osteoporosis which does not concern us today,
25 but also pain management which does concern us. I am here

1 in part today because of what I consider to be considerable
2 experience with tramadol, and in so telling you those
3 experiences, I hope to reflect any potential or perceived
4 conflicts of interest.
5 I have been involved in at least one clinical
6 trial comparing tramadol to a nonsteroidal anti-
7 inflammatory drug. I have been a paid consultant to Ortho
8 in terms of educational programs both in the design and the
9 delivery of those programs. I have written an article in a
10 peer-reviewed journal Drugs on an overview on tramadol in
11 osteoarthritis, which is a wear and tear type of arthritis,
12 and of course have used this drug and comparable drugs in
13 private practice, as I have already indicated.
14 I have not kept any official log of my use of
15 tramadol in patients with musculoskeletal diseases, nor
16 have I kept any official log for any other drug. However,
17 I want to show you an overhead of sort of an extrapolation
18 of the incidence of my use of tramadol over the years.
19 In the first year, FY 1996, we used the Ultram
20 sheet, and I'll explain that in a minute. The second year,
21 a chart review; and the third year, a sample distribution
22 log. And let me explain.
23 When the drug first came out, as is usual in my
24 practice, we prepared an information sheet on this drug,
25 and I also wanted to make sure that we would decrease some

1 of the, what I refer to as nuisance side effects such as
2 nausea, dizziness, and sedation. So, therefore, I
3 recommended to our patients that they start low and
4 gradually build up on the dosage.
5 So, every patient received an information sheet
6 and at the same time we recorded the patient's name that
7 they received that. There were some 315 patients that
8 first year that received that sheet, at least that we
9 recorded.
10 In terms of chart review, what I had my staff
11 do was take a three-month sample in the second year and
12 extrapolate those numbers to one year, and we had 396
13 patients that we had prescribed tramadol to.
14 Finally, during the past approximately four,
15 five, six months, we have kept a very, very dedicated log
16 of our sample distribution. So, we treated sampling of
17 patients just like we would as if we wrote a prescription,
18 and I've been able to extrapolate that. So, we've had a
19 total of 858 patients over the past several years who have
20 been given tramadol. Now, these are patients, not patient
21 visits.
22 The total number of patients in my opinion that
23 have exhibited clear-cut abuse have been 0. There were 2
24 patients that I will share with you that I had some level
25 of suspicion and still do not know whether these were

1 patients who were abusive, but let me tell you what they
2 are.
3 One patient was a 40-year-old with
4 fibromyalgia. For those of you not familiar, this is a
5 painful rheumatic condition frequently affecting middle-age
6 women. The patient had been to many physicians and had
7 many different medications, including nonsteroidal anti-
8 inflammatory drugs without any help. To my knowledge, the
9 patient never did take any narcotic agents.
10 The first visit after I gave her tramadol, she
11 came back and said, quote/unquote, this is a breakthrough
12 drug. I feel wonderful. It's the first drug that has ever
13 helped me. So, I was a little bit concerned that she was
14 sort of overreacting to the response of this drug. On
15 subsequent visits she sort of settled down. The only thing
16 I can tell you is this patient now has been since on
17 tramadol and has never exceeded the original 150 milligrams
18 that was recommended for her. I let you make your own
19 judgment.
20 The second patient had a very rare disease
21 called Behcet's that was characterized by very painful
22 vaginal ulcers and very painful mouth ulcers. When she
23 came back, she said, this drug makes me feel wonderful.
24 Now, I have always asked my patients whether
25 they have any out-of-the-ordinary reactions to medications.

1 I do not ask them, are you abusing the drug? That's not
2 part of what I do. But, however, when this lady said, I
3 feel wonderful, I started to explore a little bit and her
4 response was, well, of course, I feel wonderful. For the
5 first time, in two years I've been free of pain. The
6 patient subsequently discontinued the medication as the
7 ulcers disappeared and seemed to have no withdrawal
8 reactions whatsoever.
9 And that's it in terms of my experience.
10 But my real reason in testifying today is to
11 express my concern about the scheduling of this drug. I
12 look at tramadol as a niche drug. In my opinion as a
13 practicing rheumatologist, it is not a drug for everyone,
14 and I would be deceiving you if I said this is the panacea.
15 It is not. Not all patients respond to it. Not all
16 patients are free of side effects, although as I've
17 indicated before, I consider the side effects to be
18 nuisance side effects. But it definitely does fill the gap
19 of patients who cannot take nonsteroidal anti-inflammatory
20 drugs, who cannot take narcotics, or for whatever reason
21 won't take these drugs. Patients with fibromyalgia, for
22 example, this being a noninflammatory condition, may have
23 no response whatsoever to nonsteroidal anti-inflammatory
24 drugs.
25 I reported the results of a Harris pain poll

1 about a year or two ago and was impressed, as we've heard I
2 think Dr. Savage allude to, that the majority of patients
3 or so many patients feel as if their pain is untreated.
4 This is a significant number. Don't ask their doctors.
5 Their doctors, according to the Harris poll, feel as if
6 they are doing a wonderful job in relieving the patient's
7 pain, but ask the patient, and they'll say they feel
8 unrelieved. And I see Dr. Savage shaking her head yes.
9 However, when you ask these patients would you
10 take a narcotic, they were reluctant to do so. So, we have
11 what we've often referred to as the analgesic dilemma.
12 There you have patients in need of a medication and won't
13 take at least narcotics for relief. Tramadol, as far as I
14 am concerned, has helped fill that void.
15 I am concerned that scheduling will label this
16 as an addictive, abusive medication and therefore patients
17 and their doctors will be reluctant to prescribe it.
18 So, in summary, I consider Ultram to be a
19 useful drug in rheumatologic practice, rheumatologic
20 diseases, by the way, being one of the most common for
21 which patients seek medical advice, whether it be to a
22 primary care physician or an orthopedist or a
23 rheumatologist. In my experience, while the drug has the
24 so-called nuisance side effects that I mentioned before, it
25 is safe in terms of not having any organ-damaging potential

1 like bleeding peptic ulcers or liver disease and the like,
2 and in my experience with several hundred patients at
3 least, it has no abuse potential, at least not in the types
4 of patients that I'm seeing.
5 My recommendations to this committee are that
6 the drug not be scheduled because it will limit
7 accessibility to this valuable drug and will limit its
8 usefulness.
9 Thank you.
10 DR. STRAIN: Thank you, Dr. Katz.
11 I would like to suggest now that we ask the
12 sponsor actually if we might go into some questions and
13 discussion with the sponsor.
14 DR. BURTON: Certainly, by all means. Perhaps
15 if you've not got a particular person you think is a target
16 for your question, I'd be very happy to act as the sort of
17 master of ceremonies.
18 DR. STRAIN: That would be wonderful. Thank
19 you.
20 So, what I'd like to suggest now is that we
21 might -- well, let me back up a moment. Do we have any
22 other speakers for the open public hearing?
23 (No response.)
24 DR. STRAIN: So then, what I'd like to suggest
25 to the committee is that we spend a little bit of time now

1 taking an opportunity to ask the sponsor any questions we
2 might have, run till 12 o'clock with that. Then we'll take
3 a break for lunch and come back and pick up where we left
4 off on the schedule. Does that sound all right to
5 everybody? Good.
6 Questions from the committee for Dr. Burton or
7 other members of the sponsor's group? Dr. Meyer?
8 DR. MEYER: I have three questions.
9 The first I guess would be for Dr. Cicero, and
10 that is, how long should the monitoring process go on?
11 The second question I guess any of you can
12 answer, and that is, there is a difference between straight
13 withdrawal symptoms and withdrawal symptoms associated with
14 some craving response. It's not clear from anything that
15 we've read about whether anyone has actually looked at that
16 question about whether the withdrawal symptoms associated
17 with tramadol has some type of craving response associated
18 with it.
19 The last question, which I would really ask Dr.
20 Savage and maybe the group, is you've developed really an
21 alternative paradigm, and the question about whether, in
22 rethinking this, there are other drugs that you would
23 rethink with regard to this, specifically buprenorphine,
24 pentazocine, and propoxyphene.
25 DR. CICERO: To answer the last question, I

1 think they'd all be excellent candidates. One of the
2 problems we suffer is we don't have a good solid
3 comparative database for other drugs. That's one of the
4 issues.
5 With respect to your withdrawal question,
6 Roger, we clearly distinguished withdrawal per se from
7 withdrawal with craving. In fact, in withdrawal with
8 craving or other signs of drug-taking behavior, that was
9 rated as a positive case of abuse. Clearly distinguished.
10 DR. MEYER: Do you find withdrawal with
11 craving?
12 DR. CICERO: Yes.
13 Your first question was?
14 DR. MEYER: How long should this committee go
15 on?
16 DR. CICERO: As long as the company is willing
17 to pay for it?
18 (Laughter.)
19 DR. CICERO: It's indeterminate. Our
20 commitment ended after three years. We have renegotiated
21 and signed an agreement that we will continue for at least
22 another year, renewable for yearly intervals thereafter.
23 I have no idea. My own feeling would be at
24 least several more years. I think the company is committed
25 to some period of time. I can't speak for them, but my own

1 view would be it should continue for some period of time
2 until we can make some rather definitive conclusion this
3 drug simply is not going to catch on with any drug culture.
4 DR. MEYER: And that would be in all dimensions
5 of the screening?
6 DR. CICERO: Yes.
7 DR. MEYER: I'm still unclear what percentage
8 of people that have the withdrawal symptoms actually
9 experience this craving response.
10 DR. CICERO: It's a relatively small number,
11 but Ed Senay might be able to answer that question.
12 DR. SENAY: Most of the reports we get do not
13 contain information about whether there was craving or not.
14 If craving is reported, we would probably take that as
15 addictive behavior and it would flip it out of the
16 withdrawal category into the -- but I don't think we had
17 many. Out of the positive cases, I don't think we had many
18 where withdrawal was accompanied by craving. But we would
19 have flipped it into the positive.
20 DR. CICERO: It was just a handful.
21 DR. BURTON: Maybe I could offer some help with
22 your question about the withdrawal symptoms with craving or
23 without craving. If we look at the spontaneous reports
24 that we have, given all the criteria about the information
25 on the original reports, et cetera, et cetera, we do have a

1 breakdown that may go some way to answering your question.
2 Can I have that slide please?
3 These are the total number of reports of
4 withdrawal, and I think that is some indicator. I see
5 other nodding heads here that perhaps agree with a clinical
6 impression that that might be about the right number. I
7 don't think you could be any more certain or specific about
8 this.
9 In terms of how long would the committee go on
10 -- Mr. Chairman?
11 DR. STRAIN: Yes.
12 DR. BURTON: Might I perhaps just ask the
13 President of Ortho-McNeil who perhaps could give the
14 sponsor's view of this because I think that may be
15 important in your deliberations. I don't want us to be
16 seen as an uncaring organization. Would that be all right?
17 DR. STRAIN: Certainly.
18 DR. BURTON: Mr. Eric Milledge who is President
19 of Ortho-McNeil.
20 MR. MILLEDGE: Thank you, Dr. Burton.
21 I think the simple answer to the question as to
22 how long we'd continue the monitoring process is that we
23 would continue it as long as the independent steering
24 committee, Dr. Cicero, and ourselves felt that it had a
25 useful role to play. That would go on for as many years as

1 Dr. Cicero and the independent steering committee thinks
2 it's appropriate. But we are fully supportive in our
3 commitment to back that study.
4 Thank you.
5 DR. STRAIN: Thank you.
6 Other questions? Dr. de Wit?
7 DR. de WIT: I have a question for Dr. Cicero.
8 You made a point of emphasizing that the criteria for your
9 categorizing abuse -- I think this was in the key
10 informants and the grantees -- was DSM-IV criteria for
11 abuse or dependence. Is that right?
12 DR. CICERO: Yes, that's correct.
13 DR. de WIT: So, that's a fairly stringent
14 criterion for categorizing a drug. Did the patients have
15 to report that this was then their only drug of abuse?
16 DR. CICERO: No, they did not.
17 DR. de WIT: So, how did you decide to
18 categorize somebody as meeting criteria for abuse or
19 dependence of tramadol in particular?
20 DR. CICERO: If tramadol was one of the drugs
21 that they abused.
22 DR. de WIT: Ever?
23 DR. CICERO: Ed?
24 DR. SENAY: We discussed this at length and
25 felt that public health would be best be safeguarded if we

1 took the worst case scenario. So, even though Ultram was
2 most frequently accompanied by other drugs, if the person
3 met criteria for DSM-IV abuse or dependence, we called it
4 Ultram. So, we made the worst case scenario. You don't
5 get the quality of data in most reports from the field that
6 really would permit you to do much except make worst case
7 scenario judgments.
8 DR. de WIT: Do you have a sense of how often
9 other drugs then would appear by this particular reporting
10 system?
11 DR. CICERO: Yes, I don't. We could look at
12 it. Certainly the number of patients that we could
13 document abused tramadol exclusively was a very small
14 number.
15 DR. SENAY: Like 3 cases out of several
16 hundred.
17 DR. CICERO: A handful, 5 or 6.
18 DR. STRAIN: Dr. Senay said that there were 3
19 cases out of several --
20 DR. SENAY: Approximately.
21 DR. STRAIN: Approximately 3 cases.
22 DR. SENAY: Small number just (inaudible).
23 DR. STRAIN: Can you repeat your statements
24 into a microphone?
25 DR. CICERO: A small number used it for

1 sustained, exclusive use. This was multi-drug. But again,
2 we wanted to be conservative.
3 Go ahead, Harriet.
4 DR. de WIT: So, this is just mentions of ever
5 having used in patients who meet criteria for substance
6 abuse or substance dependence. Is that right?
7 DR. CICERO: It would have had to have met
8 criteria for abusing tramadol along with other drugs.
9 DR. de WIT: Abusing tramadol. How is that
10 defined?
11 DR. CICERO: Ed.
12 DR. SENAY: Let me give you a feeling for the
13 range of data that we had. We went and examined some cases
14 and in the instance of one addicted physician, he used
15 tramadol almost exclusively over a one-year period. So,
16 that was quite clear. But most of the cases abused
17 tramadol along with other drugs, and we worst case
18 scenarioed that. We thought that we just could not rule
19 out that. We had to make it the worst case to protect
20 public health. If a pharmacist or a health care
21 professional said I know of a case of Ultram abuse, then
22 that was a positive. It didn't have to be any criteria.
23 We just made the worst case scenario so no one could say
24 you guys are juggling this around or something like that.
25 We did not encounter the kinds of patterns that

1 you see with heroin and cocaine and alcohol with exclusive
2 use over a period of weeks, months, or years to produce
3 intoxication. We did not see that.
4 DR. STRAIN: Dr. McNicholas?
5 DR. McNICHOLAS: Yes. Could I just ask for
6 some clarification on a point that I think Dr. de Wit was
7 making, and that is, for instance, if you had a patient who
8 was being treated by one of your key informants for
9 alcoholism, cocaine abuse, or whatever, and they started to
10 report occasional tramadol use, would that be considered
11 abuse?
12 DR. CICERO: Yes, it would.
13 DR. McNICHOLAS: Thank you.
14 DR. STRAIN: Dr. Young.
15 DR. YOUNG: I have a question for Dr. Cicero
16 about your stimulated reporting system. If I understand
17 you correctly, you have about 250, 255 key informants --
18 DR. CICERO: Correct.
19 DR. YOUNG: -- that include NIDA grantees and
20 other individuals working in substance abuse.
21 DR. CICERO: That's right.
22 DR. YOUNG: How frequently are these
23 individuals surveyed?
24 DR. CICERO: Quarterly, with instructions to
25 contact me in between time if they pick up any cases, which

1 they do quite frequently by e-mail.

2 DR. YOUNG: What percentage of your surveys are

3 returned?

4 DR. CICERO: 52.6 percent with a range of 48.7

5 to 54.3.

6 DR. YOUNG: And how has that changed over the

7 three years? I gather you are now in your fourth year.

8 DR. CICERO: It has not decreased at all.

9 DR. YOUNG: What percentage of your informants

10 have returned all surveys?

11 DR. CICERO: I don't have the answer to that

12 question. Quite often informants will only return surveys

13 when they have some response to make. I don't know, Alice.

14 I don't know.

15 DR. YOUNG: The intent of my question is to

16 have an idea of is it the same 52 percent who are

17 returning.

18 DR. CICERO: No.

19 DR. YOUNG: What proportion of these

20 individuals, of the key informants, are in primary basic

21 research settings? Perhaps that might be the NIDA grantee

22 population.

23 DR. CICERO: I'd say most of the NIDA grantees

24 are what I would call basic science. They're at an

25 academic center doing research.

1 DR. YOUNG: But not necessarily with access to
2 a patient population.
3 DR. CICERO: They would all have access to
4 patient populations.
5 DR. YOUNG: And what proportion of the 255 fall
6 in that group of basic researchers and what proportion are
7 in service delivery?
8 DR. CICERO: I'd say 50 percent are in the
9 former category and 50 in the latter.
10 DR. YOUNG: Thank you.
11 DR. CICERO: Those are rough numbers.
12 DR. STRAIN: Other questions? Dr. Khuri.
13 DR. KHURI: This is for Dr. Cicero also. I'm
14 interested in your slide on tramadol abuse and dependence
15 in cases with history of drug and alcohol abuse in which
16 you showed 66 percent of the total positive for opiates and
17 13 percent positive for drugs and alcohol.
18 Now, that was a little confusing to me and it's
19 related to Dr. de Wit's series of questions. The opiates
20 in this case were not other opiates used for pain. These
21 were assumed to be abusers or just multiple users of other
22 opiates?
23 DR. CICERO: They were assumed to be abusers.
24 DR. KHURI: Just by the fact that there were
25 other perhaps non-prescribed opiates?

1 DR. CICERO: They usually reported a past
2 history or a current history of abuse of other drugs,
3 alcohol and opiates.
4 DR. KHURI: This brings me to really my main
5 concern which is a professional concern of mine of pain
6 management in former abusers, recovering people,
7 alcoholics, methadone-maintained patients. I'd like you to
8 comment on that.
9 DR. CICERO: Well, when the Dear Professional
10 letter went out -- I'll demonstrate the independence of the
11 committee. We disagreed strongly with the company sending
12 out the letter with respect to the wording because they
13 really discouraged its use in people with a prior history
14 of drug abuse. Our recommendation was that physicians be
15 strongly warned of the potential for a low level of abuse,
16 so if you're going to use it in these populations, at least
17 monitor it very carefully. That was prompted by a large
18 number of phone calls. And believe me, in answer to your
19 question, Alice, there's no reluctance on the part of these
20 informants to call me or e-mail me in between survey
21 periods.
22 I got a very angry response to the letter
23 saying, how dare you take away one medication I can use. I
24 use it in my methadone clients routinely and it's an
25 extremely effective medication. And now you're telling me

1 I can't use it. Well, no one said you can't use it.
2 Well, the company was dissuading use in that population.
3 I would differ with that position. I think our
4 committee would differ with that position. A physician
5 should use caution in using it in that population and look
6 out for abuse. It concerns me a little bit when a
7 physician makes the statement and I think we heard, with
8 all due respect, in the open session someone indicated this
9 was not a narcotic. It's a great drug to fill into a
10 niche. That attitude worries me. I think physicians
11 should acknowledge the fact it has some abuse potential,
12 and if you're going to use it in someone who's on methadone
13 or going to use it for someone who has a past history, use
14 it very carefully being cognizant of the fact there could
15 be a potential problem here.
16 But let's not overestimate the problem. I
17 think we have 247 cases. It's a strong drug history in
18 that. We don't have any idea how many drug-experienced
19 individuals or people with a history of opiate abuse have
20 used Ultram successfully. We have no way of gauging that
21 number. My suspicion is, from the self-reports we've
22 gotten, most physicians are not having any problems with it
23 at all.
24 DR. KHURI: It does make one wonder whether it
25 might not be a more effective pain manager in methadone-

1 maintained patients because of it being not simply a mu
2 agonist, the mega-doses of morphine overcoming the level of
3 tolerance.
4 DR. CICERO: Three methadone clinic directors
5 that I am aware of have informed me exactly that. That's
6 their theory.
7 DR. KHURI: That's what I would guess.
8 Thank you.
9 DR. STRAIN: Other questions?
10 Dr. Cicero, I had one actually. Did the
11 independent steering committee consider there was a problem
12 in March of 1996? One of the points that has been made is
13 that this provides a real-time assessment of what's going
14 on. If I recall from your figure, March 1996 looked like
15 things were going on the up and up, and was something done
16 at that point?
17 DR. CICERO: Yes. The committee had alerted
18 the company there was an FDA meeting at the time where we
19 raised these concerns. We had begun to identify the
20 populations that -- the drug history that indicated a
21 severe issue and withdrawal.
22 If there's still a lesson to learn about
23 withdrawal, the label for Ultram must much more clearly
24 specify how to taper this dose, as we do with all other
25 medications because what we still find physicians doing is

1 keeping the patient on high dose tramadol for a long period
2 of time, and then for whatever reason, they just tell them
3 to stop and a very mild opiate withdrawal syndrome ensues
4 in the next two or three days. Then you get back to them
5 and say, well, you didn't taper. You would taper a beta
6 blocker. You would taper other drugs. So, I think the
7 label actually needs to be strengthened. That would
8 eliminate about 50 percent of, quotes, abuse, if you
9 consider withdrawal abuse. And it is causing discomfort to
10 patients.
11 DR. STRAIN: So, there were meetings held with
12 the FDA and there was some discussion about that.
13 DR. CICERO: Correct.
14 DR. STRAIN: And then one other question, if I
15 could. Dr. Katz' comments. The two cases that he
16 described as suspected abuse or possible abuse, would you
17 have put them in your category of --
18 DR. CICERO: No.
19 DR. STRAIN: -- alleged or --
20 DR. CICERO: They would have been negative.
21 DR. STRAIN: Well, because you've got a
22 clinician who's saying that there may be abuse going on.
23 DR. CICERO: In those particular cases, the
24 facts as he described them, I think they would have gone
25 down as a negative. I didn't hear anything in those cases.

1 He was suspicious about something, but when he probed it,
2 the person stated, I feel great because my pain is
3 relieved. I doubt seriously our committee would have rated
4 that as alleged for abuse. They're nodding no. So, I
5 don't think we would have rated --
6 DR. STRAIN: So, he was indicating that there
7 was some flag in his mind as a clinician that there was
8 something unusual.
9 DR. CICERO: I interpreted his comment to say
10 he got suspicious, but then as he explored the
11 circumstances, he became non-suspicious. Is that correct?
12 DR. KATZ: Yes.
13 DR. CICERO: It was followed up and there was
14 no additional problems. So, therefore, we would certainly
15 not have scored it as positive. It was follow-up
16 information.
17 Eric, we get a lot of those. In the beginning
18 especially, I had people checking off or e-mailing me,
19 because we made it as simple as possible, a response saying
20 I've just seen dependence. I called the physician. This
21 is embarrassing, but I called the physician and he had seen
22 12. So, I called him and said, I don't understand. And he
23 said, well, I really want to participate in this study.
24 I'm glad to do it, but I've go these 12 people. I said,
25 well, explain what you've got. And he goes, well, I was

1 getting to their pain now, and they need it for their pain
2 relief. So they're, therefore, dependent on it. This is
3 the kind of issue we got into more, and I said, they're
4 dependent on it for its pain relief. He goes, well, yes,
5 that's dependence. Well, that isn't dependence.
6 DR. SENAY: Can I make a comment?
7 DR. CICERO: Yes, please. Just come up to the
8 microphone, Ed.
9 DR. SENAY: One of the things that we did that
10 you haven't heard of yet is to improve the data acquisition
11 process at the point of receipt -- we created sheets that
12 we enhanced the information that we got. So, we tried to
13 gather data, like if Dr. Katz had sent in I'm suspicious,
14 we would have probably tried to get back and say, did you
15 follow up? And if said, yes, I followed up, there was no
16 problem, I know this patient now over a six-month period,
17 we would have called that a negative. But if he had just
18 told us I suspect there's a problem, it would have got in
19 on the positive side. Once again, we went by the worst
20 case scenario. What would your mother say is what guided
21 us.
22 (Laughter.)
23 DR. SENAY: I don't know what your mother would
24 say. My mother would say, Edward, if they say it's Ultram,
25 it's Ultram.

1 DR. STRAIN: We won't bring my mother into this
2 meeting.
3 (Laughter.)
4 DR. CICERO: Right. I think again we want to
5 underscore that. We were extremely conservative. With
6 some of the cases of alleged, as you read through them, I
7 think you would scratch your head and say, would that even
8 remotely fall in the category. But again, our goal and our
9 commitment to the public health argued that we would always
10 err on the side of being much, perhaps too, conservative.
11 DR. BURTON: Mr. Chairman, may I suggest that
12 there was a question that alluded to the use of tramadol in
13 I think known abusers of the drug, and perhaps you'd
14 consider Dr. Jasinski who works in this field, and I feel
15 sure he may have a comment that might prove helpful and
16 useful for the committee members. Is that all right?
17 DR. STRAIN: Please.
18 DR. CICERO: I feel also very certain Don will
19 have a comment on anything.
20 (Laughter.)
21 DR. JASINSKI: I just go back to pharmacology
22 which is the queen of medical sciences.
23 (Laughter.)
24 DR. JASINSKI: I seriously say this because the
25 question of dependence is always the issue. We know that

1 in certain animals, if you do this, if you make the animal
2 dependent and you stop it, for example, you can create a
3 need state from withdrawal. That data was from Dr.
4 Yanagita. With measuring break points, you can do this.
5 So, the question is, does tramadol have the
6 capacity to do this? It's unclear in humans. We didn't do
7 it, but there were some studies which were done by McNeil
8 in the pain populations and Dr. Richter looked at the drug
9 when it was used in relatively large doses for period of
10 time. My understanding is he did not see any withdrawal,
11 and I think he even attempted to precipitate with naloxone.
12 So, that issue is that again, consistent with
13 the pharmacology, you probably -- staying in the
14 therapeutic doses, even taking the data that I had in terms
15 of assuming this is mu agonist effects, are going to get a
16 very low level of mu agonist effects.
17 You deal with the other issue, which Graham
18 alluded to for looking at this, which is the issue of -- we
19 have the same problem in the benzodiazepine issue and we
20 argue about this. Those people who actually look in the
21 real world come back in, and we now talk about
22 discontinuation or termination reactions because -- and
23 this was also alluded to by the clinician -- is when you
24 stop the drugs, you not only get the physiologic process of
25 withdrawal, you get a loss of the pharmacologic action

1 which is an emergence of pain and the biologic pain
2 response plus a behavioral disruption. When somebody has
3 been learned and getting this and you take away the drug,
4 you get a behavioral disruption.
5 The other issue I think was, Graham, we had a
6 discussion. We met yesterday -- is that coming to this
7 meeting, I met with my staff. We had our staff meeting
8 last week, and they said, where are you going? I said, I'm
9 going next week to the FDA. They said, you're going away
10 again? And to the FDA -- and they're talking about
11 controlling Ultram. And they said, don't do it. Okay,
12 tell them they can't do it.
13 And the reason is that a few years ago, for
14 about five years now, we take care of high risk patients.
15 We have a primary health care clinic for the medically ill
16 addict and alcoholic of which about 400 are HIV/AIDS
17 patients, intravenous drug users. In this population --
18 and as the addict population ages, even though staying in
19 treatment, they get lots of aches and pains and primary
20 care. We have a clinic in which if you have a controlled
21 prescription blank, those are locked up. I mean, we
22 prescribe no controlled substances at all in this
23 population, the high risk population.
24 The drug of choice, when you look at this, if
25 you eliminate any of the mu agonists, even propoxyphene,

1 you're left with nonsteroidals. And the nonsteroidals have
2 a lot of problems. If you take nonsteroidals chronically,
3 there are lot of medical problems, especially in a
4 population who are taking triple therapy, have all sorts of
5 other illnesses to use nonsteroidals.
6 When you look at this among all of the drugs
7 for an analgesic, the only centrally acting analgesic you
8 have that has a nonopioid-like action, that has a low abuse
9 potential, and in our experience has caused no problems is
10 tramadol. I mean, I think that really puts it into the
11 real world.
12 And we don't see people taking it and going up
13 to those doses that we gave experimentally when a high risk
14 population is given to it.
15 We also have a medical detoxification program,
16 2,500 people a year -- 2,500 admissions a year. We haven't
17 seen any tramadol in the five years.
18 Our experience is common with most people's
19 clinical experience, to put it in perspective.
20 DR. STRAIN: Thank you.
21 Dr. de Wit. Oh, I'm sorry. Dr. Burton, did
22 you have another?
23 DR. BURTON: No.
24 DR. de WIT: Before you sit down, Dr. Jasinski,
25 I have a question for you.

1 DR. JASINSKI: I figured either Harriet or
2 Alice would get me.
3 (Laughter.)
4 DR. de WIT: You went through the data quite
5 quickly where you were doing abuse liability studies
6 comparing the drug oxycodone, which you said has a high
7 liability for abuse, to tramadol. On that slide before you
8 went to the metabolite issue, you're showing that there are
9 similar responses on opiate identification, MBG scores, and
10 liking. In fact, the graph there shows that the liking
11 ratings are pretty much comparable, and this is not just in
12 the time to response but in the maximum response.
13 DR. JASINSKI: Yes.
14 DR. de WIT: So, how do you resolve that? How
15 do you kind of reconcile that with saying that this has a
16 lower abuse potential than oxycodone?
17 DR. JASINSKI: If you look at that, Harriet,
18 that's a dose of 700 milligrams of tramadol. That's 14
19 unit doses. That means that if somebody was going to take
20 this and you abuse it chronically if they would do it three
21 or four times a day, 14 times 4 is what? 56 tablets a day
22 times a week. So, I don't think anybody is going to go
23 into looking at this as a sustained level.
24 The issue which is here has been that so that
25 this is again just like Ted. We produced the worst case

1 scenario, going up to seeing the maximum tolerated sort of
2 dose. If you go into what would be the therapeutics or
3 even two or three multiples of the therapeutic dose, you're
4 not seeing any evidence which we were able to see, any
5 evidence of mu-like agonist effects.
6 So, the answer is yes, if people were to take
7 in the range of probably 10 to 14 tablets -- or 8 to 14
8 tablets, they can get a mu-like agonist effect. However,
9 the effect is much delayed -- is delayed in terms of hours
10 -- so that if you go between the behavior and the
11 reinforcer, there's a delay even in the worst case.
12 There have been probably people who've gone up
13 to this dose level, but the experience, as I understand it,
14 is very clear. If you take the stuff and inject it, you
15 don't see any mu agonist effects. It only occurs in humans
16 -- it has only been demonstrated when it has been given
17 orally in what would be 8 to 14 times the therapeutic dose.
18 Is this the metabolite? I wish I could make a
19 clear statement, yes, it's the metabolite entirely, but the
20 data is not consistent because these effects don't sort of
21 covary with the metabolite and plasma.
22 DR. de WIT: I agree that the time to the onset
23 of the effect may be an important factor in whether it's
24 likely to be abused. But from your data here, it looks
25 like you do get significant increases in liking scores at a

1 relatively low dose. In fact, the drug-abusing population
2 is notorious for taking many times more than the prescribed
3 dose anyway. So, I'm not sure that's an argument against
4 its likelihood for abuse.
5 DR. MEYER: Don't sit down.
6 DR. CICERO: Can I just indicate that these
7 clinical trials are simply predictive? In our own draft
8 guidelines of the FDA, epidemiological data take precedence
9 over it. I don't know what Dr. Jasinski was finding, but
10 clearly we have not seen that in a real life situation.
11 DR. de WIT: All right.
12 DR. STRAIN: Dr. Meyer? Were you done, Dr. de
13 Wit?
14 It may be useful to show that slide if it's
15 possible.
16 DR. JASINSKI: Harriet, the issue which is here
17 is things are relative. In an absolute sense, yes. In the
18 worst case, if I can do it, and I pushed the dose to doses
19 that probably no one else would push it up to get these
20 sort of effects.
21 The real issue was that this -- things are
22 relative. All we can do is compare this to other drugs.
23 If you take propoxyphene as the prototype, as the mu
24 agonist of what we regard as the pure mu agonist of least
25 abuse potential, there is clearly a dissociation that the

1 doses we use for analgesia for propoxyphene on a relative
2 potency, there is no selectivity for propoxyphene. This
3 drug, the doses we use and the mechanisms we use to produce
4 analgesia are probably not mu agonists. If we push the
5 dose, we can see mu agonism.
6 So, what we always do is say, yes, this has a
7 lower abuse potential relative to, okay? Even relative to
8 oxycodone in terms of analgesic doses, this is still the
9 same issue, and this is just pushing the dose.
10 And this is the maximum liking score which is
11 here. This is the point I was making. This is 175
12 milligrams which is three to four times the therapeutic
13 dose.
14 DR. STRAIN: That's actually time.
15 DR. JASINSKI: Time. I'm sorry.
16 So, this is not significantly different from
17 placebo because they overlap. So, it's only when you get
18 up into this range which is 7 to 14 therapeutic doses do
19 you get significant detection of signal, whereas I can give
20 you -- I can pick up a couple of Darvons.
21 DR. MEYER: That's the question. My point is
22 clearly this is not a schedule 2 drug, but it's not clear
23 that it's not a schedule 4 or a schedule 5 drug in terms of
24 buprenorphine or pentazocine or propoxyphene. You've
25 looked at all these three drugs. And it's not clear to me

1 how this drug, in terms of everything that you usually look
2 at, really differs from those three drugs.
3 I would turn the question also the other way
4 relative to Dr. Savage and that is you have a warning
5 that's gone out from the company. It's not clear that the
6 advisory committee's function and its more intensive
7 monitoring -- how well known that is in the community.
8 But I think one of the issues that she was
9 talking about, in terms of physicians being discouraged by
10 the scheduling process, is the monitoring issue. But
11 essentially you're doing monitoring at one level.
12 So, how do you differentiate? Is this drug
13 really different?
14 DR. JASINSKI: Yes.
15 DR. MEYER: In the things that you've looked at
16 relative to those schedule 5 drugs, not morphine, not
17 oxycodone --
18 DR. JASINSKI: Can we go back to the very first
19 slide?
20 Are you asking this of me or are you asking --
21 DR. MEYER: I'm asking of you how this drug
22 fits into those other three drugs that you've studied well.
23 DR. JASINSKI: Okay. When we had this, if you
24 take this, if you look at the data for codeine, which is an
25 example --

1 DR. MEYER: I wanted the other three drugs.
2 You've looked at buprenorphine and --
3 DR. JASINSKI: Okay. If you take the data for
4 buprenorphine, our data for relative potency for euphoria
5 and miosis for buprenorphine is identical to the analgesic
6 potency estimates that Ray Hood got in those dose ranges.
7 It's identical. Alice is shaking her head. There is no
8 selectivity. Buprenorphine selectivity comes in because
9 it's a partial agonist when you push the dose.
10 Pentazocine, which has been studied -- and even
11 Eric, I think after we did, recognized that pentazocine is
12 a mixed drug in that in the low doses in the therapeutic
13 dose that pentazocine produces its analgesic activity
14 through a mu agonism. If you stay in the range of about 40
15 milligrams of pentazocine, it looks just like 10 milligrams
16 of morphine. When you push the dose, the kappa effects
17 come in.
18 Propoxyphene is impotent and propoxyphene, if
19 you stay within the doses -- and there are three sets of
20 experiments, the original Luxon experiments, and then I did
21 IV propoxyphene, and then I did this when -- pushed very
22 large doses because our colleagues in California discovered
23 that propoxyphene was one methyl group away from methadone.
24 And they were having trouble using methadone in California,
25 and they discovered if they gave large doses of

1 propoxyphene, they could use this as a maintenance drug.
2 One of the things that occurred, they were
3 having seizures all over the place. And we used to go to
4 meetings. Most of you remember those days where they would
5 talk about how the seizures were inconsequential in this.
6 They'd fall in the clinic and they would have seizures all
7 over the place.
8 But again, propoxyphene. There is no
9 dissociation of its analgesic and mu agonist effects.
10 Now, we have a series of drugs -- I think Dr.
11 Savage pointed out -- where we have drugs which have
12 multiple modes of action. The classic example is
13 meperidine. Meperidine in therapeutic doses is a mu
14 agonist. As you go up in dose, you begin getting
15 anticholinergic effects, and if you're aware of the
16 literature, you can get an atropine psychosis with
17 meperidine.
18 Now, with both propoxyphene and meperidine, you
19 have the active drug. The initial drug is a mu agonist.
20 They have metabolites which have an additional toxicity
21 which have a longer duration which account for the seizure
22 activity seen with meperidine and propoxyphene, which is a
23 relatively common event.
24 Now, looking at this, if you now come back in
25 and look at what makes tramadol different, the parent

1 compound is not a mu agonist. It's reversed. If it
2 occurs, the mu agonism is not in the analgesic. The major
3 effect we're dealing with is at the level of a drug which
4 is producing it through a different mechanism.
5 What reverses is when you push the dose, you
6 see the mu agonism. So, when you look at this versus
7 pentazocine or propoxyphene or even meperidine, those drugs
8 are mu agonists, and then when you push the dose, you see
9 the other actions.
10 With tramadol, the major action is probably
11 serotonergic, noradrenergic uptake. The parent compound is
12 probably the convulsant, and when you push the dose, if it
13 is the metabolite, that's when the mu agonism comes in.
14 Does that answer your question?
15 DR. MEYER: Yes.
16 DR. STRAIN: Dr. Cicero, did you want to make a
17 comment?
18 DR. MEYER: I guess Dr. Savage is going to
19 answer the second part of the question.
20 DR. CICERO: I was going to address Roger's
21 point as well. I don't think our data support at all that
22 this looks like another schedule 4 or schedule 5. I don't
23 know what frame of reference you would have to make that
24 sort of comment.
25 But I guess my ultimate point would be to say

1 perhaps -- remember back to the original conceptualization
2 of this project in 1994 that --
3 DR. MEYER: I wasn't on the committee.
4 DR. CICERO: Yes, I know. But to refresh your
5 memory or --
6 DR. MEYER: I read the material, yes.
7 DR. CICERO: Yes. I think the notion was, in
8 fact, the nonscheduled status would essentially produce no
9 more abuse than a schedule 4 or 5, and that's precisely
10 what we're finding. There is no more abuse with this
11 compound being nonscheduled.
12 And I would suggest to you maybe there are --
13 and it was my answer earlier -- some other schedule 4 and 5
14 drugs that we ought to be -- instead of just reflexively
15 scheduling, have a post-marketing surveillance program,
16 spend the money, as this company has done, and look, and
17 then you'd have comparative data. So, it's an important
18 distinction, but I think it needs to be made.
19 DR. STRAIN: Dr. Savage?
20 DR. SAVAGE: Yes. I think Dr. Jasinski really
21 answered your question, but I would just emphasize from a
22 clinical point of view that I think we don't know why there
23 is such low abuse found with tramadol completely. We don't
24 know all the mechanisms that create that low abuse of the
25 drug.

1 But I think we can't underestimate the effect
2 of the delayed onset of the liking response in a vulnerable
3 population and to remember that Dr. Jasinski's studies were
4 done in an addict or an abuse population. So, they were
5 prone to liking. So, certainly in our pain patients for
6 whom we're using this, I think the risk of developing
7 craving and that repetitive use in high doses that may
8 create addiction is very, very unlikely because the delay
9 in the onset of the reward.
10 DR. MEYER: The question I thought you were
11 going to answer was with the letter from the sponsor to the
12 medical community with the heightened warning with regard
13 to abuse liability that came out with that letter -- and it
14 was unclear to me whether the practicing community was
15 aware of the intensive monitoring that was going on --
16 whether you would see this as -- I mean, how you
17 differentiate this in terms of the degree to which it might
18 discourage analgesic prescribing relative to a schedule 4
19 or schedule 5 because you presented this issue around
20 schedule 4, schedule 5, or scheduling of drugs as
21 discouraging analgesia prescription.
22 DR. SAVAGE: How the awareness of the
23 monitoring might discourage --
24 DR. MEYER: And the warning, when the warning
25 came out, that it essentially said --

1 DR. SAVAGE: Don't use in individuals with
2 addiction.
3 DR. MEYER: In people who might be at risk.
4 DR. SAVAGE: Well, I have to say that I don't
5 agree with that approach. I think that we need to use --
6 this drug in particular has value in working with people
7 who have addictions.
8 DR. MEYER: Right.
9 DR. SAVAGE: I think that physicians, treating
10 individuals with histories of addiction and abuse, need to
11 be cautious in the prescribing of all medication.
12 The only people I have in my practice who use
13 20 Motrin 600 a day, ibuprofen 600 a day, are people with a
14 history of abuse and addiction. I think that addicts are
15 prone to overuse many chemicals, including what we would
16 consider nonabusable medications.
17 But I would just caution docs to be careful in
18 using this with people with histories of addiction, but not
19 make it not available.
20 DR. MEYER: No. You're still missing the
21 point. You've made the point that scheduling of a drug
22 discourages appropriate prescription for analgesia.
23 DR. SAVAGE: Yes, I believe it does.
24 DR. MEYER: You now have a drug which is not
25 scheduled but which has a monitoring system in place, which

1 has a warning label in place with regard to risk of abuse
2 and addiction. To what degree do you see those two
3 components as a discouragement for analgesia, and how would
4 you rate that as a discouragement for analgesia
5 prescription relative to scheduling it in schedule 4 or
6 schedule 5?
7 DR. SAVAGE: I don't know the answer to that
8 because --
9 DR. MEYER: I'm asking you as a clinician.
10 DR. SAVAGE: As a clinician, I don't see that
11 it has impaired people's prescribing of the medication at
12 all. I think that concerns regarding regulatory scrutiny
13 are regarding licensing or regarding sanction by local
14 medical boards and that level of scrutiny that really
15 deters doctors. I haven't been aware of doctors hesitating
16 to prescribe tramadol because of any awareness, though I'm
17 not sure they are aware. But I don't believe coming from
18 academics, people doing research, people monitoring the
19 drug, that would have an impairing effect. If anything, I
20 think it might have a facilitatory effect.
21 DR. STRAIN: Dr. Burton, did you have a comment
22 on that?
23 DR. BURTON: Just a comment for that question.
24 Warning letters and labeling associated with a product are
25 there to provide information to physicians. I'm sorry.

1 I'm teaching you to suck eggs. But they're there primarily
2 for information purposes, and of course, they can have a
3 very variable effect on prescribing habits with physicians.
4 Even I was fairly fickle as a prescriber when I got warning
5 letters from the companies in the past.
6 So, it's a very unpredictable effect, although
7 clearly Dr. Cicero had a few phone calls and lots of e-
8 mails complaining about that letter when it went out. I
9 suspect that that happens whatever the letter that goes out
10 informing the prescribing community about potential
11 pitfalls.
12 DR. STRAIN: Dr. Andorn, last question.
13 DR. ANDORN: Well, two questions, if I may.
14 One is I notice you're keeping data on the
15 number of new prescriptions and repeat prescriptions. Can
16 you share with us the proportion?
17 DR. BURTON: I think Dr. Gibson may have some
18 information on that. Dr. Gibson is one of the physicians
19 in Ortho-McNeil with responsibility for tramadol.
20 DR. GIBSON: Our data suggests that about 60
21 percent of the use is for chronic use and 40 percent for
22 acute.
23 DR. ANDORN: Thank you.
24 And my second question is does anyone know if
25 tramadol is on the VA formulary, national formulary?

1 DR. GIBSON: I believe the answer is no.
2 DR. ANDORN: And if not, why not, if anybody
3 has a feel for why not, if it is not on the VA national
4 formulary?
5 DR. GIBSON: I don't have the answer to that.
6 DR. STRAIN: I'm sorry. Make that the
7 penultimate question. Dr. Frank.
8 DR. FRANK: Dr. Cicero, may I ask you a couple
9 of questions?
10 I had an opportunity last night to look at your
11 June 1997 report and then your update to December 1997.
12 That period of time -- I don't know whether it's catching
13 up with past data, but there seemed to be a lot more
14 reporting by December 1997 than June 1997. Is that a
15 function of how you're updating your information?
16 DR. CICERO: It reflects the quarterly report
17 due in September 30th. Our data run in three-month spurts.
18 So, what you saw in June was the -- the June 30th data was
19 current through the survey date of June 30th. The next
20 survey would have been September 31st. Is that right?
21 DR. FRANK: September 30th.
22 DR. CICERO: Whatever. It would have been at
23 the end of that quarter, and it takes us about six to eight
24 weeks to turn around. That would be the updated data. So,
25 every quarter we get a surge of cases coming in.

1 DR. FRANK: Because the impaired health care
2 professionals, in 1997 there were I believe 88 such cases,
3 and then in December 1997, there were I think 113
4 cumulative so that that seemed to be a big spurt for that
5 six-month period. Everything seemed to go up about 15
6 percent, 20 percent. You mentioned the key informants in
7 New Orleans. That was a spurt. But was this the beginning
8 of a cycle?
9 DR. CICERO: Almost all the cases you see with
10 the numbers coming in -- no, I don't believe it was the
11 beginning of a cycle. In fact, if I look at this quarter
12 through the end of March -- the data aren't complete yet
13 because we're still getting the surveys in -- indicate even
14 less than it was in the fourth quarter of 1997.
15 DR. FRANK: The DAWN data. Are you going to
16 look at the geographic distribution or can you of those --
17 to validate any of your findings?
18 DR. CICERO: We have certainly asked and
19 requested that information. To the best of our knowledge,
20 it is not available. It has not been analyzed. It has not
21 been published. It is not available.
22 DR. FRANK: Because that would be an
23 interesting validation tool for you.
24 DR. CICERO: The very first question the
25 committee asked is, what more information can we get from

1 that? In fact, the most immediate question we would have
2 is, are we seeing the same thing? Are we getting some
3 cross-reporting there? That was number one. Number two,
4 if we're not, that raises a whole series of other issues to
5 look at.
6 But we can't get any data. There's no data.
7 That limited value of it for us.
8 DR. FRANK: I think there was an error on your
9 DAWN slides showing the rate per prescriptions comparing
10 codeine to tramadol. Codeine was one of the drugs. I
11 think the denominator should have been in millions, not
12 thousands.
13 DR. CICERO: No, that's not true. That's
14 codeine only. That's not codeine preparations. That's
15 what's astounding. That's codeine only.
16 DR. FRANK: Codeine only.
17 DR. CICERO: That is not tylenol and codeine.
18 That's just codeine.
19 DR. FRANK: And that there were only 85,000?
20 DR. CICERO: Prescriptions for codeine per se,
21 no codeine preparations now.
22 DR. FRANK: Thank you.
23 DR. STRAIN: I'd like to suggest that we take a
24 break for lunch and reconvene here in one hour. Thank you.
25 (Whereupon, at 12:08 p.m., the committee was

1 recessed, to reconvene at 1:08 p.m., this same day.)

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1 AFTERNOON SESSION

2 (1:08 p.m.)

3 DR. STRAIN: Let's go ahead and get started

4 then.

5 Was there anybody who wished to speak for the

6 second portion of the open public hearing?

7 (No response.)

8 DR. STRAIN: If not, we'll go then to the FDA

9 presentations and begin with the regulatory history being

10 presented by Dr. John Hyde.

11 DR. HYDE: Thank you. My remarks are going to

12 be fairly short. I just am going to give some background

13 on the history and the events and thinking that led up to

14 our being here today. There is a short chronology in your

15 meeting package.

16 Originally this advisory committee met in

17 August of 1994 to consider the scheduling issue for

18 tramadol. At that time some data were presented. There

19 were some abuse liability studies similar to what you've

20 seen today.

21 Also there was available some epidemiology.

22 Tramadol had been a drug approved in Germany at that time,

23 17 years before the advisory committee met, and there had

24 been about 11 million prescriptions written in Germany, and

25 it was also available in some other countries. There were

1 about 100 reports, a little over 100 reports, of possible
2 abuse that were presented at that time. Some of them were
3 not all that well documented.
4 Also at that time the sponsor presented their
5 plan for the steering committee, some studies to be done,
6 and their plan for post-marketing monitoring.
7 Basically you have the minutes of the meeting
8 in your package, but in summary the conclusions were that
9 the abuse liability was low for this drug. There was some
10 argument about whether it was significant and what that
11 really meant, but I think there was a general feeling that
12 there was a low potential for abuse.
13 Also the sponsor's plan that was presented to
14 the committee alleviated most of the concern to the degree
15 that the recommendation was that scheduling really didn't
16 seem to be required at this time.
17 Subsequent to that, the sponsor somewhat
18 refined their post-marketing plan, committed to performing
19 that. Some other issues and review had to be completed,
20 and the drug was finally approved in March of 1995, a
21 little over three years ago.
22 Now, the original labeling of the drug is in
23 your package under the approval letter, but I just want to
24 call your attention to some of the parts that are
25 particularly pertinent to today.

1 This is the drug abuse and dependence section
2 as it was in the original labeling. Basically it mentioned
3 that there was a possibility of some drug dependence and it
4 mentioned codeine and dextromethorphan as comparators, but
5 also described little real experience or real evidence of
6 abuse in the foreign clinical experience; that there could
7 be some opiate effects at high doses; and that there might
8 be tolerance but it was probably unlikely and, when
9 present, really wasn't very severe. And it explained a
10 little bit of the pharmacology which was relevant to the
11 abuse potential.
12 It also mentioned that at that time the assay
13 for tramadol wasn't included in the routine urine screen.
14 Another part of the labeling was in the
15 precautions section, and this had to do mainly with the
16 concern that tramadol wouldn't really substitute for
17 opioids and that if someone were physically dependent on
18 opioids and were transferred over to tramadol, that they
19 might actually experience withdrawal symptoms because of it
20 not substituting.
21 Over that first year, 1995, we began to get
22 some reports that suggested that there was abuse and
23 dependence. In particular, the reports of tolerance, some
24 cases of withdrawal, overdoses, some cases of prescription
25 shopping, and seeking treatment for taking tramadol. By

1 the end of 1995, there had been about 100 reports or so
2 received in the spontaneous reporting system, and at that
3 time there had also been a couple million, I think about 3
4 million prescriptions for tramadol written.
5 That was enough to make us feel that there was
6 something at least that we needed to modify in the labeling
7 because it was qualitatively a little different from what
8 we might have expected from the 17 years of German
9 experience.
10 So, early in 1996 the FDA and R.W. Johnson had
11 some meetings and we worked out some revisions to the
12 labeling. I should mention there was another issue that we
13 were watching besides the abuse potential and that was risk
14 of seizures. So, we made some revisions then to the
15 labeling, and in March of 1996, about one year after it was
16 approved, a Dear Doctor letter was sent out describing the
17 changes in the labeling. This in part relates to the
18 increase in reporting. That's a natural sequelae of such a
19 thing. So, that is at the same time as you notice the
20 increase in reports.
21 This tries to contrast the original labeling
22 with the current labeling, which is also in your package.
23 The wording was modified somewhat and strengthened to
24 indicate that we thought there was a definite possibility
25 of tolerance development and a little strengthening of the

1 warning in particular. We mentioned the reference was
2 changed to dependence of the morphine type to indicate mu
3 opioid and describing that there had actually been reports
4 of craving, drug-seeking behavior, and tolerance.
5 And also the recommendation that it not be used
6 in opioid-dependent patients because we had seen some
7 reports of dependent patients reinitiating their dependence
8 after using tramadol. So, the recommendation was if there
9 was a history of drug abuse, chronic use of opioids, that
10 tramadol was not recommended.
11 By that time, there was an assay, not part of
12 the opioid, but assays were available for it. So, that
13 particular statement was dropped from the abuse and
14 dependence section.
15 In addition, a warning was added reflecting
16 pretty much what was in the abuse and dependence section,
17 in particular, that there could reinitiate physical
18 dependence and the recommendation that it not be used in
19 those patients. That was a recommendation that was not put
20 in the contraindications section.
21 As I mentioned, subsequently there was an
22 increase in reports of both seizures and abuse and
23 withdrawal. That took the time course that you've seen in
24 the previous graphs. But by the end of 1996 and into early
25 1997, after that sort of reporting surge had leveled off,

1 there were still reports of abuse and seizures. So, we met
2 again, had a series of meetings actually with the company
3 in late 1996 into early 1997.
4 In February and March of 1997, we asked to be
5 updated on the actions and findings of the steering
6 committee and also discussed that year would be about the
7 third anniversary of the advisory committee meeting and we
8 thought it would be a good idea to review the scheduling
9 decision to see what we had learned, to see if the
10 recommendations still held up. Also at that time work was
11 begun by the FDA on the eight-factor analysis.
12 As it turned out, because of scheduling
13 considerations, we really couldn't meet in 1997. We
14 originally had set to have this meeting in February of
15 1998, but because of some late data, we had to postpone it,
16 and then the SAMHSA data, the DAWN data. The meeting was
17 then rescheduled for today and that brings us to where we
18 are now.
19 DR. STRAIN: Thank you, Dr. Hyde.
20 Next we'll hear from Dr. Klein who will present
21 an introduction to the issues.
22 DR. KLEIN: Some of this is going to be
23 repetitious from what Dr. Hyde presented in the regulatory
24 history.
25 As Dr. Hyde stated, when tramadol was approved

1 in 1995, the issue of the drug's abuse potential was
2 brought before the Drug Abuse Advisory Committee. The
3 committee discussed the issue and some concern was raised
4 that the drug, after marketing, would be abused. In
5 preclinical and clinical studies, the drug demonstrated
6 some activity that was typical of mu opioids.
7 However, the drug was not recommended for
8 scheduling and this was largely because there was this long
9 marketing history of tramadol in other countries, primarily
10 Germany, and the sponsor maintained that there was very
11 little actual abuse of the drug so as not to result in any
12 sort of public health problem. In addition, the sponsor
13 maintained that tramadol had a "low abuse potential."
14 The drug was approved and in place of
15 scheduling the drug under the Controlled Substances Act,
16 what was put into place were a series of recommendations by
17 this committee establishing a risk management plan. The
18 key elements of this strategy encompassed acquiring
19 knowledge about the use and abuse of the drug, surveillance
20 of abuse problems, instituting intervention plans should
21 abuse be found, and proposed mechanisms for resolution.
22 This has been termed the ISC, the independent steering
23 committee.
24 Now, on the issue of the possible scheduling of
25 tramadol, we are required to address eight factors. These

1 eight factors, as you can see, cover a myriad of aspects
2 dealing with the drug. This includes pharmacology, basic
3 science issues, as has been reviewed earlier, and
4 information that would be acquired from other data
5 gathering systems, including information from the
6 independent steering committee. Then the recommendation
7 for scheduling would be considered.
8 These recommendations are always based on
9 relative abuse potential; that is, this is the regulatory
10 course that follows under the Controlled Substances Act.
11 You have comparator drugs, and you compare the unknown drug
12 to comparator drugs. A statement of low abuse potential
13 really has minimal use.
14 Now, our recommendations are based on
15 scientific and medical data, as I say, and issues related
16 to the abuse and use of the drug.
17 Now, we've never made a scheduling
18 recommendation without having the right comparators to make
19 that recommendation. Again, these recommendations are made
20 relative to other substances. We've never controlled a
21 beta blocker. Beta blockers are not controlled under the
22 Controlled Substances Act, but what are controlled are
23 drugs which are active in the central nervous system, have
24 opiate-like, hallucinogenic-like stimulant, depressant, or
25 hallucinogenic effects. The Congress added in the early

1 1990s anabolic steroids to that category.

2 In addition, we've never made a recommendation

3 of scheduling without having some human data.

4 Now, these are the eight factors that we have

5 to address, and we always use the best data that is

6 available.

7 If the drug has an abuse potential, we seek

8 evidence of its being self-administered. We look for drug-

9 seeking behavior for craving. We look for motivation that

10 the drug might be taken outside of medical direction, such

11 as, is the drug europhigenic? Does it produce effects that

12 someone might seek out for those effects?

13 Also we look at dependence. We look at

14 dependence because it's called for. It's the seventh

15 factor of the eight factors. It's a requirement under the

16 law, and it's also indicated by a withdrawal syndrome. In

17 fact, we look for dependence and we look for a withdrawal

18 syndrome because the patient should know that he might

19 become dependent on the drug. He should know that there

20 might be a withdrawal syndrome if he takes the drug

21 chronically and then he goes off the drug and he's

22 suffering a withdrawal syndrome.

23 Now, some of the scheduling issues that are

24 relevant are pharmacologic similarity of the unknown drug

25 to other drugs that are controlled. We look for similar

1 abuse and diversion problems of the drug. We try to
2 establish a level playing field. If the sponsor has a drug
3 that's similar to other drugs that are controlled, we feel
4 that drug should be treated similarly. That's a level
5 playing field. That's what's known as fairness. And also
6 the scheduling of the drug is necessary to impart proper
7 warnings to the drug.
8 Now, for the Medwatch data, the spontaneous
9 reports of data, which will be explained later by Dr.
10 Alderfer, which includes abuse indicating COSTART terms,
11 these terms that we look at provide the signal of abuse,
12 and there are also COSTART terms, of course, that provide
13 signals for convulsions, for seizures.
14 The agency and the sponsor were sufficiently
15 concerned back at the end of 1995 and early 1996 that the
16 sponsor sent out a Dear Health Care Professional letter
17 that resulted March 20th of 1996, and the labeling was
18 revised to include stronger warnings in the labeling.
19 The Dear Health Care Professional letter that
20 went out had the warning on drug abuse, that 115
21 spontaneous domestic reports described as drug abuse,
22 dependence, withdrawal, or intentional overdose, and that
23 Ultram should not be used in patients with a past or
24 present history of addiction or dependence on opioids.
25 And then along with this, the warning seizures

1 went out. 83 domestic reports were described as seizures
2 or convulsions and seizures have been reported after the
3 first dose, at the recommended dosage range, as well as at
4 higher doses.
5 Now, we also, as I say, changed the labeling,
6 and as Dr. Hyde pointed out, we changed the labeling. Now,
7 we changed the labeling because of the events that
8 occurred, because of the reports that we received.
9 Now, some of the relevant features have, again,
10 been covered by Dr. Hyde, but it includes the statement of
11 opioid activity due to low affinity binding of the parent
12 compound and higher affinity binding of the 0-demethylated
13 M1 metabolite occurs at the mu opioid receptor.
14 On the next slide is the warning that Dr. Hyde
15 went over, that Ultram should not be used in opioid
16 dependent patient, and that Ultram may reinitiate physical
17 dependence in some patients previously dependent on
18 opioids.
19 And in the precautions section, there's a
20 warning about possible respiratory depression, the
21 withdrawal symptoms which may occur if the drug is
22 discontinued abruptly and that was described in the
23 labeling. The symptoms include anxiety, sweating,
24 insomnia, rigors, pain, nausea, tremors, diarrhea,
25 respiratory symptoms, piloerection, hallucinations.

1 On the next slide, another warning was put in
2 for labor and delivery. The chronic use during pregnancy
3 may lead to physical dependence and postpartum withdrawal
4 symptoms in the newborn.
5 And Dr. Hyde went over the drug abuse and
6 dependence portion which to my mind is a fairly strong
7 warning, that Ultram has a potential to cause psychic and
8 physical dependence of the morphine type. The drug has
9 been associated with craving, drug-seeking behavior and
10 tolerance development, and reported that cases of abuse and
11 dependence have been reported.
12 Also on the next slide, you'll see a
13 description of the overdoses which have occurred in which
14 cases of overdosage with tramadol have been reported with
15 serious potential consequences including respiratory
16 depression and seizures.
17 And then directions were given on treating an
18 overdose with adequate ventilation as supportive treatment
19 and also the statement that while naloxone will reverse
20 some, but not all, symptoms caused by overdosage with
21 Ultram, the risk of seizures is also increased with
22 naloxone administration.
23 Nevertheless, as you'll see in data that will
24 be presented by Dr. Alderfer, the Medwatch signal persists
25 through 1997. In light of that, we have the following

1 questions for the committee.

2 Dr. Burton went over this question this

3 morning. To consider the new information about tramadol

4 obtained since the last Drug Abuse Advisory Committee

5 meeting and since marketing. What are your opinions with

6 regard to the potential for abuse of this product?

7 Now, in the next slide, we have been provided

8 with some legislative guidance of what is an indicator of a

9 drug's potential for abuse. Now, there were four possible

10 definitions that were given as guidance.

11 One, there's evidence that individuals are

12 taking the drug in amounts sufficient to create a hazard to

13 their health or to the safety of other individuals or to

14 the community.

15 Or, two, there's significant diversion of the

16 drug or other substance from legitimate drug channels.

17 Or, three, individuals are taking the drug on

18 their own initiative rather than on the basis of medical

19 advice from a practitioner.

20 Or, four, the drug is a new drug so related in

21 its action to a drug or other substance already listed as

22 having a potential for abuse to make it likely that the

23 drug will have the same potential for abuse as such drugs,

24 thus making it reasonable to assume that there may be

25 significant diversion from legitimate channels, significant

1 use contrary to or without medical advice, or that it has a
2 substantial capability of creating hazards to the health of
3 the user or to the safety of the community. Evidence of
4 actual abuse of a substance is indicative that a drug has a
5 potential for abuse.
6 Question 2 is on the next slide. Are the
7 reports of clinical abuse (actual) and pharmacological
8 features of Ultram similar to other opioids which are
9 scheduled in the CSA? If so, which ones?
10 Now, on the next slide, you'll see the
11 definitions of the drugs in different schedules. As you
12 can see from schedule 1, these are drugs with high
13 potential for abuse, going down to schedule 5, where we're
14 making a relative determination, abuse relative to the
15 drugs in those schedules or other schedules. And you'll
16 see the part of the definition of each schedule deals with
17 dependence and assessment about the drug's dependence-
18 producing capabilities.
19 Finally, on the next slide, are some common
20 examples of opioids which are controlled in the different
21 schedules under the CSA. Schedule 1 includes a drug like
22 heroin. Schedule 2, morphine, oxycodone, oxymorphone,
23 hydrocodone, propoxyphene (bulk), codeine in its pure form,
24 methadone. Schedule 3 includes some preparations of
25 codeine and hydrocodone. Schedule 4, preparations of

1 dextro-propoxyphene and difenoxin, and schedule 5, some
2 more preparations of codeine and hydrocodone.
3 Now, on the next slide is the third question.
4 The agency would like to obtain the committee's comments on
5 the independent steering committee as a successful
6 deterrent to the abuse of the drug or as a useful post-
7 marketing tool to evaluate the evolving patterns of abuse.
8 And please also explore possibilities for the future
9 mission, goals, and duration of the independent steering
10 committee.
11 The agency's review in addressing these issues
12 will include a description of the preclinical predictors of
13 abuse liability, a review of the clinical abuse liability
14 studies, epidemiology data, including Medwatch data, as
15 well as DAWN data presented by SAMHSA, and an assessment of
16 the independent steering committee and the phase IV
17 studies.
18 Now, in addition, the agency, and specifically
19 our group, is involved with projecting quotas for
20 controlled substances since there has been much discussion
21 this morning about the negative impact that scheduling a
22 drug has on the medical use of the drug. This is kilograms
23 of usage for oxycodone from January of 1983 projected
24 through 1998, to the end, and you see a continuing increase
25 for the schedule 2 opiate oxycodone.

1 Here we show hydrocodone. Granted, most of the
2 hydrocodone products are either schedule 3 or 5, but the
3 bulk drug is schedule 2. Again, you can see an increase in
4 the usage of hydrocodone from 1983 through to 1998.
5 Of course, the standard morphine. Again, we
6 have an increase in usage of morphine, a schedule 2 opiate,
7 from 1983 through to 1998.
8 So, the scheduling of these well-used opiates
9 has had virtually no impact that I can see on the overall
10 usage of the drug in medical practice.
11 Could I have the next slide please? Before we
12 do that, we have some handouts for the committee and the
13 sponsor. We just prepared this on Friday and it's listings
14 of products containing four drug substances which are
15 controlled in schedule 2. You can see all the opioids
16 there that are on the market for oxycodone, hydrocodone.
17 Meperidine is in the list. I'm not quite sure what else is
18 in the list. But you'll see that there are many products
19 on the market that are controlled.
20 Now, we don't routinely monitor the Internet.
21 Occasionally we will just go there in a non-rigorous
22 approach just to see what's happening with certain drugs.
23 I have some statements here from physicians on line just to
24 show you some of the statements that you see regarding the
25 use of Ultram.

1 Now, the first one is dated April 17, 1997.
2 This is from a physician -- I've taken the names out -- in
3 which the physician says, I've treated patients that have
4 abused Ultram. One particular patient that I am aware of
5 was a medical student that was taking 1,500 milligrams per
6 day. His history was such that he had previously abused
7 other drugs, other controlled opiates. Ultram does not
8 show up on the usual drug screens and is more readily
9 available from new physicians who do not believe that it
10 can be addictive or can give an addict a buzz.
11 Ultram withdrawal is typical of other opioid
12 withdrawals and does not respond to typical withdrawal
13 medications used for opioid withdrawal.
14 And then another statement on April 19th. As a
15 medical director of an inner city methadone program, I've
16 seen significant abuse of Ultram by my addict population.
17 They use it as a substitute for opiates or to enhance the
18 effects of heroin and/or methadone by ingesting 5 to 10
19 pills at a time in addition to their prescribed methadone
20 or narcotic analgesic. They appear to like the
21 benzodiazepine side effect, as well as the opioid effect.
22 Currently it is highly sought after because it is readily
23 prescribed by naive doctors unaware of the abuse potential.
24 That's all. The next presentation will be
25 given by Dr. Brase.

1 DR. STRAIN: Thank you, Dr. Klein.

2 Dr. Brase will be speaking on the pharmacology.

3 DR. BRASE: Well, now that Dr. Burks has given
4 you the mechanism of action of the drug in animals by many
5 different routes, including ones that are not relevant to
6 the oral administration of tramadol in humans, I would like
7 to concentrate on the preclinical data which suggest that
8 tramadol has an abuse liability.

9 I would first like to start by just briefly
10 summarizing what was presented at the 1994 DAAC committee
11 meeting by Dr. Harry Geyer who was the original reviewing
12 pharmacologist for the NDA of this drug. What he noted was
13 that tramadol has active metabolites, not just one but two,
14 M1 and M5, but we know very little about M5. But with
15 regard to M1, it is a major metabolite in several species.
16 It has up to 200 times the potency of tramadol in drug
17 receptor binding assays in which it has a fairly high
18 affinity for opioid mu receptors as opposed to delta or
19 kappa receptors, which have also been studied. And it
20 appears to be a full agonist in that in the tail flick test
21 it seems to have fairly steep dose-response curves when
22 given by the systemic route.

23 In terms of dependence liability, there haven't
24 been any drug discrimination studies with the drug.
25 Tolerance studies in mice yielded mixed results. There was

1 one study where the ED50 did not change over a period of
2 several weeks. There were a couple of other studies in
3 which there was about a three-fold tolerance developed to
4 tramadol in mice.
5 Withdrawal has been studied in both mice and
6 rats. With chronic treatment, one can show a withdrawal
7 syndrome with tramadol but in comparison with morphine, it
8 is not quantitatively the same. The intensity of the
9 withdrawal signs are less with tramadol dependence than
10 with morphine dependence, but qualitatively the same kinds
11 of signs are observed in rodents.
12 Now, in studies with monkeys, tramadol neither
13 precipitated withdrawal in morphine-dependent monkeys, nor
14 did it suppress withdrawal in morphine-dependent monkeys.
15 These were monkeys that were maintained on a dose of 3
16 milligrams per kilogram 4 times a day. So, it's a fairly
17 high level of physical dependence. Under those
18 circumstances, tramadol was not able to suppress
19 abstinence-induced withdrawal.
20 However, when monkeys were given the
21 opportunity to self-administer tramadol, they would self-
22 administer it if the dose was 1 milligram per kilogram.
23 They would not self-administer it relative to saline if the
24 dose was one-tenth of that, 0.1 milligram per kilogram.
25 This was studied in 4 monkeys and of those 4 monkeys, 1 of

1 the monkeys self-administered tramadol compulsively to the
2 point where it induced seizures and despite having seizures
3 and deteriorating in health, it continued to self-
4 administer tramadol until it died in the third week of
5 testing and this was a 5-week testing paradigm.
6 Finally, Dr. Geyer mentioned that the naloxone
7 pA2 value for tramadol in mice -- and this was with the
8 mouse tail flick test -- was the same as that for morphine,
9 which implies that the drug has mu receptor dominance, at
10 least in this test. What you have to remember is all the
11 pA2 value is is a negative logarithm of a dose in moles per
12 kilogram that causes the ED50 of the agonist to double. If
13 one is dealing with kappa agonists, the pA2 value is
14 usually below 7, 6 point something, whereas with mu
15 agonists, it's above 7. In the case of tramadol, it was
16 around 7.7 or 7.8.
17 I'd like to talk a little bit about the
18 metabolism of tramadol. There are three major metabolites
19 in man. Five metabolites have been identified using carbon
20 14 labeled tramadol. The species difference was done quite
21 a long time ago. It was published by Linz in 1981. But
22 what it demonstrates is that here's man. There were only 2
23 subjects that were given the radioactive one. There's a
24 more recent study reviewed by Dr. Raffa that involved 9
25 patients that were missing their gallbladders, but let me

1 first talk about this study here.

2 What we find is that for these three

3 metabolites, M1, M2, and M5, which are the major

4 metabolites, M1 is due to the O-demethylation of tramadol

5 by cytochrome P450 2D6, and M2 is an n-monodemethylated

6 metabolite that is produced by the action of cytochrome

7 P450 3A4. What recent studies have shown is that certain

8 drugs like fluoxetine will block both of these, and if they

9 block both of these, then they will block also the

10 formation of M5 which is both an O-demethylated and

11 n-monodemethylated metabolite.

12 But each one of these constitutes about one-

13 fifth of the dose given to man and also in the rat it's

14 very similar. The biggest difference between the rat and

15 the man is that man excretes probably about one-fifth of

16 the drug unchanged, whereas the rat metabolizes the drug

17 more extensively.

18 In these patients down here as well, about one-

19 fifth of the drug is excreted unchanged and another one-

20 fifth or so of the drug is excreted as M1, both free and

21 conjugated. So, M1 is not necessarily a minor metabolite

22 of tramadol.

23 Now, at the request of the FDA, the sponsor did

24 some receptor binding screening studies for a number of

25 receptors because we were also interested in trying to find

1 out whether there might be a receptor mechanism for the
2 seizures that were occurring. The only thing that really
3 stood out was the opiate receptor binding study which was
4 done with tritiated naloxone which is a less specific
5 ligand for the mu receptor than would be tritiated DAMGO.
6 Also, these were screened at a very high
7 concentration of 10 micromolar which really represents
8 overkill, but at least they did screen several metabolites
9 that had not been screened before and what we find among
10 the major metabolites is that M1 completely inhibited the
11 binding at a concentration of 10 micromolar and M5 almost
12 completely inhibited binding of tritiated naloxone at 10 to
13 the minus 5th molar. These were quite a bit more effective
14 than the parent drug itself or either enantiomer. The plus
15 enantiomer was more effective than the minus enantiomer.
16 These are three binding studies that have been
17 published since the last DAAC committee meeting on
18 tramadol. The first one is by Codd and others of the
19 sponsor, then Frink and coworkers, working for Gruenenthal
20 in Germany, and the third one is an academic collaboration.
21 But this one is kind of interesting because it was done
22 with cloned human mu receptors that were grown in a
23 neuroblastoma cell in culture.
24 What I've done is I've put these in order of
25 decreasing affinity. In other words, the higher the Ki,

1 the less the affinity or less the ability to inhibit the
2 binding of tritiated DAMGO which is an enkephalin analog,
3 fairly stable analog, with very high affinity and
4 selectivity for the mu receptor. All three of these
5 studies also looked at delta and kappa receptors, but the
6 drugs listed here all had one-tenth or less the affinity
7 for delta or kappa receptors as they did for the mu.
8 Codd actually screened about 20 drugs. I don't
9 have them all there. I put in a few just for comparisons,
10 but of these drugs, tramadol had the least affinity of all
11 of them. In fact, it had affinity less than that of
12 dextromethorphan, less than that of codeine. This tells us
13 something because it is now very clear that the analgesic
14 effect of codeine in man has, as an obligatory step, the
15 demethylation of codeine to morphine. So, even though
16 codeine has submicromolar affinities here, at least in the
17 rat brain, it is essentially inactive as an opiate in man
18 at the usual analgesic dose. I wholeheartedly agree with
19 Dr. Jasinski when he said this morning that the parent drug
20 of tramadol is not a mu agonist, at least not in man.
21 Now, among the metabolites, plus M1 and minus
22 M1 have been studied, and quite clearly minus M1 falls down
23 below codeine and dextromethorphan. So, the only compound
24 that really has a reasonably high affinity for the mu
25 opiate receptor is the plus M1 enantiomer. Of course, we

1 don't know about M5 because that has only been studied at
2 one very high concentration. But to put plus M1 in the
3 right ball park, it looks like it's in the same ball park
4 of affinity as would be hydrocodone and dextro-
5 propoxyphene.
6 Here was a study in which we're comparing the
7 affinity of the mu opiate receptors, the Ki's as reported
8 by Lai and coworkers that were on the last slide except
9 these are even more significant digits here. What we have
10 is a PK study in 18 healthy male subjects. What I've done
11 here, these are the concentrations in plasma at the Cmax
12 for plus M1, minus M1, plus tramadol, and minus tramadol.
13 One can clearly see that of these four
14 congeners, plus M1 has the smallest concentration of the
15 four. However, relative to its potency at the mu receptor,
16 which is expressed by this ratio after single dose, quite
17 clearly the overwhelming majority of the activity relative
18 to the -- or the concentration relative to the activity
19 favors the plus M1 congener over the other three.
20 Similarly, after a whole week of dosing with multiple
21 dosing, what we have is an accumulation, just about a
22 doubling of every one of these congeners after a week of
23 100 milligrams four times a day. But the same relationship
24 holds true for this ratio of Cmax over potency for
25 inhibiting DAMGO binding at the mu receptor. Again, the

1 overwhelming weight goes toward the plus M1.

2 Now, that's in terms of binding, but what about
3 in terms of some physiological function? Fortunately, what
4 we have is an electrophysiological study that was reported
5 in 1993 by Sevcik and coworkers using the spontaneous
6 firing rates of rat locus coeruleus neurons in an organ
7 bath, and the locus coeruleus contains about 1,500 cell
8 bodies for noradrenergic neurons. This is a very nice
9 model because these neurons contain both mu opiate
10 receptors and alpha 2 noradrenergic receptors which serve
11 essentially the same function. They both lower cyclic AMP
12 levels and they both increase potassium conductants, and
13 this increased potassium conductants acts as a voltage
14 clamp and serves to decrease the firing rate of these
15 neurons.

16 What we have here is the relative potency in
17 terms of the inhibitory concentration 50 again plus M1 was
18 the most potent. In terms of ability to block the
19 inhibitory effects of these with antagonists of the mu or
20 alpha 2 receptor, what we find is that the effect of plus
21 M1 was completely blocked with just naloxone. The effect
22 of minus tramadol was completely blocked with just the
23 alpha 2 antagonist, and then minus M1 and plus tramadol
24 required the presence of both antagonists to completely
25 block their effects. So, of these four compounds, only

1 plus M1 has a purely opiate mechanism of action in here.
2 Now, if we compare again the potency to PK data
3 in the rat, what we find again is that the ratio of the
4 Cmax to the potency of the IC50 again very strongly favors
5 plus M1 as carrying the bulk of the activity after a single
6 dose in rats. And similar kinds of things can be made with
7 multiple dose of PK as well.
8 So, what does this all mean? Well, first of
9 all, from the data that was presented in 1994, we know that
10 tramadol has a lower abuse liability in animals than does
11 morphine. But in terms of more recent information, what we
12 can say is that M1 and M5 are major metabolites of tramadol
13 after systemic administration. Many of the mechanistic
14 studies have been done after intrathecal administration, in
15 which case you're bypassing the liver and you're not
16 forming any active metabolites.
17 Both of these metabolites have higher affinity
18 for mu receptors than does tramadol.
19 Plus M1, at least from the electrophysiological
20 studies, appears to be a full agonist of mu opioid
21 receptors, totally blocked by naloxone.
22 Because of its relative high affinity for
23 opiate receptors compared with minus M1 or plus tramadol or
24 minus tramadol, I would have to conclude that plus M1 is
25 likely the major mediator of the abuse and dependence

1 liability of tramadol, although one cannot rule out at this
2 point a possible role for plus M5 or M5. We don't know
3 whether it's plus or minus because that is produced in
4 almost the same quantity as M1. So, I would think that in
5 a person who is a poor metabolizer of drugs that are
6 substrates for 2D5, tramadol would not have any abuse
7 liability because you wouldn't be forming any plus M1. On
8 the other hand, you might wind up with a lower ability of
9 the drug to produce analgesia as well.
10 DR. STRAIN: Thank you, Dr. Brase.
11 Next we'll hear from Dr. Cerny regarding the
12 review of abuse liability studies and Dr. Permutt as well.
13 DR. PERMUTT: I'm Tom Permutt. With your
14 permission, Mr. Chairman, I'll speak first.
15 Together with Dr. Cerny, I've reviewed the
16 double-blind phase of Dr. Jasinski's abuse liability study
17 of intravenous tramadol. We've looked at the same data as
18 Dr. Jasinski and reached very different conclusions and I
19 think I need to tell you a little bit about how.
20 An abuse liability study poses a rather
21 different kind of statistical problem than the sort of
22 pivotal efficacy studies that we're accustomed to bringing
23 before advisory committees. It's a little different from
24 much of what you have seen, and I'd like to ask you to
25 change gears in looking at it.

1 If you can't see the numbers in these tables,
2 don't worry. Actually there aren't any numbers in these
3 tables.
4 (Laughter.)
5 DR. PERMUTT: The whole point of these tables
6 is the shape. I've put outcome variables horizontally and
7 subjects vertically. A typical efficacy study is tall and
8 thin. We have one or a very few primary measures of
9 efficacy and a relatively larger number of subjects, and
10 the statistical problem is then to summarize the data for
11 each outcome variable, that is, in each column. We
12 calculate means, for example, by treatment group. We look
13 at how different groups are on average. We calculate
14 standard errors, do significance tests on the differences
15 between groups. Then having summarized the data in each
16 column, from a statistical point of view we're done pretty
17 much.
18 Now, abuse liability such as this one is
19 different. It's necessarily different. It's short and
20 fat. There are relatively few subjects; 10 in fact in this
21 study. And a lot of outcome variables. I haven't counted
22 them exactly but I'm pretty sure there are at least 500 --
23 really 500 -- without any clear primary ones. We can and
24 Dr. Jasinski has, I believe, summarized the data in each
25 column here. You can do means and standard errors and

1 significance tests. But there are some problems in
2 interpretation.
3 First of all, the summaries, being based each
4 of them on 10 subjects, are not very reliable. This is
5 especially true as regards negative results. So, you can
6 find no statistically significant difference between
7 treatments, for example. It's very difficult to draw any
8 meaningful conclusion from such a negative finding.
9 Second and more fundamentally, having
10 summarized the data in each column, in this case we're not
11 done because we're left with hundreds of summaries to make
12 sense of, and there just aren't any good statistical
13 techniques for making sense of hundreds of summaries.
14 There's a third problem with this kind of
15 analysis in this case which I think will only become
16 apparent when you've seen some of the data.
17 So, instead Dr. Cerny and I thought it might be
18 more useful to summarize the data by row rather than by
19 column. That is, we looked at subject number 1. We looked
20 at all the data for subject number 1, and we tried to say
21 what happened to subject number 1. What was his experience
22 in this trial, and what happened to subject number 2? And
23 it still leaves us 10 summaries to deal with, one for each
24 subject, but not 500. Besides I think there is in fact
25 some coherence in the 10 summaries.

1 So, what did happen to these 10 subjects?
2 Well, 3 of them did not respond to intravenous morphine. I
3 don't know why. They didn't feel it. They didn't like it.
4 They didn't get high. And those 3 didn't like tramadol
5 either.
6 The other 7 did respond to morphine. 3 of
7 those 7 didn't like tramadol, and the other 4 did like
8 tramadol, at least at the 200 milligram intravenous dose.
9 When I say they like it, I mean they responded positively
10 to the questions, do you feel an effect, do you like the
11 drug, how high are you right now? And in addition, 3 of
12 the 4 identified the effect as like an opioid.
13 So, to conclude, if you look at means, you can
14 conclude that on average tramadol is between morphine and
15 placebo. You can even say for some variables that tramadol
16 is not statistically significantly different from placebo,
17 but as I said, it's not a meaningful statement to make with
18 samples of this size.
19 If instead you look at what happened to these
20 10 subjects, one at a time, I think you can draw a more
21 meaningful conclusion. Tramadol for some subjects was not
22 like morphine at all. For other subjects, tramadol was
23 like morphine, and for those subjects, it was in fact very
24 much like morphine.
25 DR. STRAIN: And now we'll hear from Dr. Cerny.

1 DR. CERNY: As Dr. Permutt had stated, we
2 jointly reviewed Dr. Jasinski's intravenous study.
3 This was performed in 1992-1993, issued in
4 1995. The purposes were -- I won't bore you with too much
5 of this -- to determine a maximal safe dose of intravenous
6 tramadol. These were in male subjects with an opiate abuse
7 history. It also estimated its abuse potential compared
8 with that of morphine and placebo.
9 There were two segments, a single-blind and
10 double-blind portion, an n of 6 in a single-blind, and they
11 gave tramadol up to 400 milligrams IV ascending order.
12 As Dr. Permutt has already stated there were
13 numerous observations from a quarter hour all the way to 24
14 hours post dose, numerous questionnaires where a subject
15 would rate on a 4-point scale, from not at all to a lot,
16 how do you feel the effect, how much do you like the
17 effects you're feeling, how much do you dislike the
18 effects, and how high are you?
19 Also included in this were the ARCI subscale
20 which included the MBG, which is a measure of euphoria, and
21 in that, unlike the previous scale which was on a 4-point
22 scale, this was a top score of 16; also the PCAG scale
23 which measures sedation, and the lysergic acid diethylamide
24 scale which measures dysphoria.
25 Also included were numerous other not only

1 objective but subjective tests such as observer drug rating
2 questionnaire, the subject drug ID questionnaire. The
3 subject would try to identify what drug this felt most
4 like. The subject-specific drug effect questionnaire,
5 which queried about symptoms; and the observer-specific
6 drug questionnaire, which queried about signs.
7 This is the mean data from the single-blind
8 portion, an n of 6 here. The subjects were asked, how do
9 you feel, like the effect?
10 You notice in the placebo part, there isn't
11 much liking, feeling, disliking, or high at all.
12 Morphine 20 milligrams, you can differentiate
13 that from placebo pretty well in that they feel the effect,
14 they like the effect. Not much disliking going on in they
15 are high.
16 You will note that the tramadol 100 milligrams
17 is similar to placebo, but as you begin to increase the
18 dose across the line, you see for feel the effect that
19 gradually increases with dose. Liking the effect gradually
20 increases with dose. Disliking the effect also gradually
21 increases with dose, and the how high are you also
22 increases with dose as well.
23 One thing interesting about these data were the
24 MBG findings which look at the measure of euphoria. You'll
25 notice they don't react for anybody, placebo, morphine,

1 nobody. Interestingly enough, in the adverse reactions
2 query the side effect of euphoria did show up in some
3 subjects for, for example, the tramadol 300, but yet the
4 MBG remains still which is an interesting observation about
5 these data.
6 To sum up the single-blind, what happened is
7 that 6 subjects were in the study. Three of them liked
8 morphine. Three had rally no reaction to morphine. Of the
9 3 that liked morphine, 2 didn't like tramadol. One
10 actually did like tramadol, got high from it, and
11 identified it as an opiate. Of the 3 that had no reaction
12 to morphine, 1 also had no reaction to tramadol. One,
13 however, like tramadol, got high, and thought it was an
14 opiate, and one sort of had a mixed reaction, liked it at
15 times, disliked it at times, was high, and identified it as
16 an opiate. So, there were subjects here, this one, this
17 one, and this one, that did appear to like tramadol.
18 Now, the original study was intended, as I
19 said, the single-blind was to go to fairly high doses, up
20 to 800 milligrams. That was abandoned because at 300
21 milligrams a subject experienced a seizure.
22 The double-blind segment -- these ex-opiate
23 abusers were to receive tramadol 400 milligrams in a Latin
24 square design. The fourth subject who received tramadol
25 400 milligrams had a seizure however.

1 So, the study was amended into a five-treatment
2 double-blind Latin square design where the subjects got
3 relatively lower doses of tramadol compared to the earlier
4 segments, the 100 and 200 milligram IV, compared to
5 morphine 10, 20, and placebo. The addiction potential was
6 assessed as previously discussed.
7 I should point out these are AUC scores.
8 You see not much of an effect of the placebo
9 overall.
10 You look at morphine 10 and 20 now. As you
11 increase the dose of morphine, you see a near doubling of
12 the feel the effect, a near doubling of the like the
13 effect, not much change in disliking the effect, and the
14 how high are you, more than doubling there.
15 The tramadol 100- and 200-milligram, as you
16 increase the dose, you did see an increase in feel the
17 effect. You also saw an increase in like the effect. You
18 also saw a slight increase in dislike the effect and also
19 an increase in the how high are you.
20 Also, with these subjects, you'll note the MBG,
21 the measure of euphoria here.
22 For placebo it was not much happening here at
23 all.
24 You look at it compared to morphine 10 and
25 morphine 20, you saw as you increased the dose, a gradual

1 increase in the MBG euphoria scale.

2 Interestingly enough, for tramadol these

3 numbers slightly decreased the MBG scale as you increased

4 the dose.

5 But interestingly enough, you look at the

6 euphoria for the adverse events reported and although the

7 morphine 20 milligram had a very high MBG score compared to

8 tramadol 200, you look at the number of euphoric events for

9 tramadol 200 milligrams, it's 12 out of the 14 subjects

10 versus morphine where 13 out of the 14. So, once again

11 there's some inconsistency apparently in some of the data.

12 Now, as Dr. Permutt pointed out, we ventured

13 into the area of looking at the individual subjects to see

14 how they reacted because as you might have seen on the

15 slides, some of the standard deviations were really huge

16 and we are measuring only a small amount of subjects.

17 Subject number 78. What I measured here is

18 liking/disliking tramadol 200 on the MBG. So, liking,

19 disliking on the 4-point scale, there was none. The

20 subject had no reaction to tramadol. This subject felt and

21 liked morphine also only a little bit.

22 Subject number 81, also liking and disliking

23 tramadol. There wasn't much of a reaction at all. The MBG

24 scale really didn't change much either.

25 Subject number 87 felt and liked morphine 10 a

1 little bit and morphine 10 moderately. You'll notice once
2 again for the liking/disliking tramadol 200, not really
3 much of a change from 0.
4 Subject number 88 didn't like really any of the
5 drugs, had no response to morphine, tramadol, or anything,
6 had a little blip here with tramadol, but really no effect
7 for any of the agents.
8 Subject number 80, I present on the top part of
9 this screen, had a profound initial dislike for tramadol,
10 followed by really no reaction. The bottom also shows
11 number 80, but this now includes the MBG subscale. You may
12 recall the liking/disliking scales are on a 4-point scale
13 and MBG runs only up to 16. You saw some moving about
14 here, probably no essential change, a little bit of an
15 increase, a little bit of a decrease there.
16 Subject number 82 is fairly interesting,
17 initially a profound 4 on a 4-point scale disliking of
18 tramadol, but as you move down to subject number 82, we
19 include the MBG scale. You'll note that after they stopped
20 disliking it, they kind of began to like it. It went from
21 around 1 to 8, sort of an interesting blip that coincided
22 with the decrease in the dislike.
23 This subject liked morphine a lot and also
24 initially liked tramadol fairly well until settling down
25 into a minor level. Number 84 -- I'm sorry. This is the

1 same subject you saw -- during this coinciding of the
2 increase of the tramadol, you saw an increase in the MBG.
3 So, there was a slight increase in the euphoria scale
4 there.
5 Number 85 also liked tramadol fairly well, a
6 moderate amount.
7 And lastly, these two subjects, 86 and 91
8 seemed to enjoy tramadol fairly well initially, a slow rise
9 about the 3-hour point hitting the maximum 4 on a 4-point
10 scale, maintaining itself for nearly 10 hours before
11 leveling off at 24. Not much change in the MBG. And also
12 number 91 liked it for about 10, 12 hours before some
13 disliking occurred.
14 And this slide I basically borrowed from Dr.
15 Permutt. This is the summary of the IV double-blind
16 segment, 10 subjects here. To summarize all those
17 individual data I showed you, 3 didn't like morphine
18 appreciably, but they didn't really react to tramadol
19 either. 7 did like morphine. 3 didn't like it; 4 did like
20 it, and of those 4, a fair amount identified it as an
21 opioid as well.
22 Included in your advisory committee packet is
23 this study from Dr. Jasinski also in the early 1990s, the
24 abuse potential now of oral tramadol. Once again, ex-
25 addicts were studied. Once again, there were two segments,

1 a single-blind and a double-blind segment. The single-
2 blind featured escalating doses up to 750 milligrams of
3 tramadol and oxycodone, the 40-milligram. Segment number
4 two featured a double-blind crossover with tramadol up to
5 700 milligrams, oxycodone 20, 40, and placebo. As you saw
6 in the IV data, one subject had to discontinue the double-
7 blind portion due to a seizure.
8 Once again we're going to run through the
9 individual subjects to give you an idea, as Dr. Permutt
10 stated. The purple here is the oxycodone 40-milligram.
11 You'll note initial liking. This is for liking the drug.
12 Oxycodone increased to 3 then 4 on a 4-point scale for a
13 while before leveling off. You'll note, however, on the
14 tramadol really no effect for the first 3 hours, and then a
15 gradual lazy rise to a fairly moderate amount of liking.
16 This is the same subject now, but I've included
17 the MBG, which I mentioned is on a 16-point scale.
18 Initially hanging around about 8, 7 to 6, and then as the
19 increase in tramadol liking began, there was a gradual rise
20 in MBG scale all the way up to 13 or so on a scale.
21 Subject number 2. This gets a little messy.
22 This includes liking, disliking, and the MBG. For most of
23 these, disliking isn't much. In this case, there was a
24 slight dislike of tramadol, followed by none whatsoever.
25 The oxycodone rises to about a 2 on a 4-point scale, and

1 the tramadol also rises to a 2, sustaining for a longer
2 period of time.
3 Subject number 3 really liked oxycodone, peaked
4 at a level of 4 on a 4-point scale for a number of hours,
5 liked the tramadol less so, but nonetheless did like it.
6 Number 4 is sort of a reversal of number 3
7 where the subject liked oxycodone a moderate amount, but
8 then really liked tramadol for a while before leveling off.
9 You'll note the MBG. This is the same subject.
10 As the subject began to like tramadol, there was a peak in
11 the MBG from 2 to about 11 or so before settling back down.
12 So, there was a euphoric effect with that dose.
13 Subject number 5 liked both drugs quite a bit,
14 a 4 on a 4-point scale. The tramadol once again took a
15 little bit of time to get to that point, although it did
16 sustain itself more so than the oxycodone did.
17 Subject number 6. This is also sort of a messy
18 slide. There was some disliking of tramadol going on, but
19 a rise of oxycodone to a 2 on a 4-point scale, and then a
20 rise of tramadol also on a 2-point scale. So, similar
21 effects with both drugs.
22 Sort of summarizing this for you, in the
23 single-blind oral portion there were 6 subjects. 5 liked
24 oxycodone; 1 liked it somewhat. 5 also liked tramadol; 1
25 liked it somewhat. 5 of the 6 were high and did identify

1 it as an opiate on the opiate scale.

2 These are summary data from the double-blind

3 portion. What's interesting here is that this was on a 4-

4 point scale and this was oxycodone 40 milligrams, and since

5 commercially it's mostly available in 5-milligram tablets,

6 these are 8 approximately of those 8 tablet equivalents.

7 You notice this being the mean data for feel the effect.

8 The oxycodone 40 rises to a peak near to and then gradually

9 levels out. The oxycodone 20 rises and then gradually

10 levels off. The tramadol 700 kind of lazily makes its way

11 to a peak, but very similar looking curves, and the same

12 thing true with the tramadol 350, a gradual rise, a peak at

13 about 6 hours until it also gradually levels off.

14 Now, for liking the drug, you'll notice a

15 dramatic initial like for oxycodone 40, a very initial

16 peak, and that sustained itself before leveling off. Also

17 a fairly quick initial rise in the oxycodone 20 milligrams

18 before leveling off. For the tramadol 700 milligram --

19 these are the triangles, dotted -- a very, very lazy

20 gradual rise till about 4 hours, but a sustaining of this

21 effect, and the same thing true with the tramadol 350, a

22 very lazy, gradual rise until that effect sustaining

23 itself. The tramadol 175, very similar to placebo.

24 The MBG I show you. This is very messy. As I

25 said, it's on a 16-point scale. You have a scale of 1 here

1 and a scale of 2 here, and you don't really see anything
2 really rising or declining very much. So, once again,
3 these data were not able to pick up really massive changes
4 in the MBG. Apparently they didn't occur.
5 This is a summary slide then of the double-
6 blind oral portion. 12 subjects on tramadol. 11 liked
7 oxycodone, but 5 also disliked it at times. One had no
8 effect from oxycodone. Now, the one who had no effect from
9 oxycodone actually liked tramadol, was high from it but did
10 not identify it as an opiate. Of the 11 who liked
11 oxycodone and 5 disliked, 9 also liked tramadol and 6
12 disliked it at times. 8 of them were high and 7 identified
13 it as an opiate. Of these 11, 2 had no effect on tramadol.
14 Neither one was high. However, one did identify it as an
15 opiate.
16 This is the last slide for me. Tramadol does
17 appear to have a lower abuse potential than morphine, but
18 it does appear to have some potential for abuse, as in some
19 parameters it behaved very similarly to the opiates,
20 especially oxycodone.
21 Tramadol's effects we have seen do appear to be
22 dose-related, and we're concerned that reports of seizures
23 will not discourage higher dose exploration.
24 And as Dr. Permutt has referred to, the studies
25 have involved measurement of really a multitude of mostly

1 subjective parameters and some of them appear to be
2 conflicting. So, certainly in future considerations of
3 studies such as these, some rank ordering of these various
4 tests would be needed.
5 Thank you.
6 DR. STRAIN: Thank you, Dr. Cerny and Dr.
7 Permutt, thank you.
8 Next we'll hear from Dr. Celia Winchell who
9 will review the phase IV study of impaired health care
10 professionals.
11 DR. WINCHELL: As Dr. Cicero mentioned this
12 morning, among the activities undertaken by the independent
13 steering committee was a pair of phase IV studies of
14 specific populations. The first was a chronic pain patient
15 population in whom the drug is anticipated to be used, and
16 the other was a study of the impaired health care provider
17 population.
18 According to the report of the independent
19 steering committee -- I'm quoting -- this group was chosen
20 because they would be expected to experiment and
21 potentially misuse a drug like tramadol at a very early
22 stage after its introduction. Health care professionals
23 have relatively easy access to the drug. They also have
24 access to detailed information about its weak opiate
25 profile, its nonscheduled status, and the fact contained in

1 the original label statement that a routine urine screen
2 was unavailable.
3 The study which was undertaken was entitled
4 Tramadol Experimentation in a High-Risk, High-Access
5 Population: Impaired Health Care Professionals. The
6 principal investigator is Dr. Sidney Schnoll. Dr. Schnoll
7 enlisted the cooperation of impaired health care
8 professional programs in four states. This was an
9 observational study, the objective of which was to identify
10 and characterize abuse of tramadol by 1,500 individuals
11 participating in impaired health professionals programs.
12 Dr. Cicero has indicated that he chose not to
13 discuss this study because it's incomplete. However, we
14 and you have been provided with a preliminary report on
15 this study which describes results from 1,479 participants,
16 which represents more than 98 percent of the planned
17 sample, and we thought it would be useful to examine the
18 preliminary findings.
19 No further demographic information on the
20 participants was given or the details of the programs in
21 the preliminary report, although this information was
22 collected, and I hope we will see it in the final report.
23 I don't have the details about programs
24 participating in the study, but for general background I
25 can describe the impaired physicians program and the

1 Maryland Board of Physician Quality Assurance. I'm not an
2 expert in this. I understand Dr. Lloyd is.
3 Physicians are referred to the Physician
4 Rehabilitation Committee for evaluation occasionally by
5 self-referral, but usually by colleagues or licensing
6 authorities, and those who are diagnosed with a substance
7 abuse problem after evaluation enter into a 5-year
8 contract. This includes monitored compliance with
9 treatment and urine testing which begins at a frequency of
10 once to twice per week for the first year and gradually
11 reduces with duration of abstinence to as low as once per
12 quarter. All substance abusers are monitored using urine
13 toxicology, including those abusing alcohol only.
14 This diagram is from the briefing booklet
15 provided by the sponsor. For this study, the participants
16 provided urine samples on the schedules required by their
17 individual programs. As I've noted, in the preliminary
18 report the schedule hasn't been described.
19 All the urine samples of active participants
20 were tested using a gas chromatography, mass spectrometry
21 test that's employed at 100 nanogram cutoff for tramadol.
22 The tests were done at approved testing centers using a
23 method that was made available by Ortho-McNeil.
24 When the urine sample tested positive for
25 tramadol, the participant was contacted as part of what was

1 called a quality assurance interview, and asked to verify
2 the medications that they had taken, both prescription and
3 over-the-counter in the past 2 months to determine if
4 tramadol was prescribed. If a prescription for tramadol
5 was reported, then the prescribing physician was contacted
6 for verification.
7 Efforts were taken to ensure blinding of the
8 monitoring program and to prevent premature intervention
9 with the idea that that would alter the course of the
10 participant's behavior and would obscure progression from
11 experimentation to abuse and impede the observational
12 quality of the study.
13 This entailed having 2 additional participants
14 who did not test positive for tramadol undergo this quality
15 assurance interview each time a positive test was
16 identified.
17 A second level of surveillance, termed level II
18 surveillance, was instituted if one of these conditions
19 obtained: either the participant did not report tramadol
20 use but urine tested positive 4 times in a 2-month period;
21 if the participant tested positive for tramadol at 4
22 consecutive screenings, which for those being frequently
23 monitored might occur in a shorter period of time than 2
24 months; or if the participant was undergoing only quarterly
25 screening and had a single positive test without a verified

1 prescription.

2 These individuals were warned during what was
3 called the generic inquiry that an unknown substance had
4 been detected in the urine. Patients who had a verified
5 prescription for tramadol at that point continued to be
6 monitored and for each subsequent tramadol positive urine,
7 the prescription was verified again.

8 Patients who did not have a verified
9 prescription for tramadol at the time of level II inquiry
10 were monitored. At that point any further tramadol
11 positive urine was interpreted as evidence of abuse and
12 reported to Medwatch.

13 The event of interest, described in the report
14 as the final endpoint, was persistent nonprescribed use of
15 tramadol, and the major dependent variable was described as
16 the number of endpoints among the 1,500 impaired health
17 professionals to be enrolled in the study.

18 This is a very busy slide, probably hard to
19 read from where you are, but you have copies of it I think
20 in your package.

21 Through December 31, 1997, 1,479 impaired
22 health care professionals were enrolled in the study. The
23 sponsor reports that 113, which is 7.64 percent of that
24 total, had at least one sample positive for tramadol. Of
25 these, 67 percent did not have a legitimate prescription.

1 These were the experimenters. 18 of these 67 met criteria
2 for the level II surveillance, and at that point the level
3 II inquiry revealed 6 who reported tramadol for medical
4 purposes, 7 who admitted to tramadol use without
5 prescription, and 5 who did not report tramadol use.
6 These last two groups, these 12, were described
7 as engaging in extensive experimentation. The sponsor's
8 report indicates that the 7 individuals who reported using
9 tramadol without prescription had no further tramadol
10 positive urines, but 11 people ultimately went on to meet
11 criteria for abuse of tramadol, had subsequent tramadol
12 positive urines, and were judged to abuse tramadol. I'm
13 not really clear on which of these groups these 11 people
14 come from.
15 For the purposes of assessing the significance
16 of the findings, I didn't think that using the denominator
17 of 1,479 for all the calculations was going to be
18 revealing. I thought it would be relevant to examine at
19 each level of use how many individuals went on to the next
20 level, and I thought it was notable that 60 percent who
21 tried tramadol at all were using it illicitly, that 27
22 percent of the experimenters went on to meet criteria for
23 level II significance, and that somewhere between 61 or
24 possibly 92 percent of the people who met level II criteria
25 went on to tramadol abuse. That's because I'm a little

1 fuzzy on where these 11 people came from. So, there were
2 18 at this step. That's 61 percent.
3 I also considered it relevant to calculate how
4 many people in the exposed population have used tramadol.
5 The 113 participants with at least one urine sample
6 positive for tramadol represent the exposed population, and
7 11 of these, nearly 10 percent, who tried tramadol went on
8 to meet criteria for abuse.
9 I have a number of unanswered questions about
10 this study report. Interpretation of the data is difficult
11 for a number of reasons. My first questions are about the
12 participants in the study.
13 We don't have information in this preliminary
14 report on the nature of the health care professional
15 programs or on the individuals included in the study, such
16 as length of time in treatment, previous drugs of abuse,
17 although this information is available and we'll, I'm sure,
18 be seeing it in our final study report.
19 We've seen from data presented this morning
20 that drug or alcohol abuse of any kind was a risk factor
21 for abuse, but a history of opiate abuse is particularly
22 relevant. This is an unselected population which may have
23 included people referred for treatment for abuse of
24 alcohol, stimulants, marijuana. There have been statistics
25 published in the last five years in the Maryland Medical

1 Journal from a variety of state programs which indicate
2 that the proportion of alcohol-only abusers ranges from 10
3 to 30 percent, some as high as 50 percent; stimulant
4 abusers, 10 to 20 percent. So, I look forward to seeing in
5 the final study report how many of the people entered into
6 the study were in treatment for opiate abuse or had a
7 history of opiate abuse.
8 The next issue is that participants were not
9 characterized with respect to duration of abstinence.
10 Typical programs can be as long as five years in length and
11 are reported to have extremely high success rates. I'm
12 told in Maryland the program has about a 75 percent rate of
13 return to medical practice and had a 3 percent rate of
14 relapse among their participants last year. So, many of
15 the study participants may have been in treatment for
16 several years and may have had firmly established sobriety.
17 Perhaps the final study report can provide us some
18 breakdowns on length of time in treatment.
19 Finally, compared to the general public or
20 certainly to the population of substance-abusing physicians
21 who are not yet in treatment, participants in the study may
22 have been at somewhat lower risk for experimentation with a
23 new drug because they are in intensive treatment and
24 regular monitoring. Conventional wisdom holds that
25 impaired physicians programs are successful because

1 participants have a great deal at risk and are highly
2 motivated to avoid loss of their licensure.
3 And even if the participants believed that
4 their use could not be detected through urine toxicology, a
5 positive urine is not the only risk of experimenting with
6 the drug. There's also the risk of loss of control over
7 the substance abuse problem. After all, alcohol isn't
8 detected in routine urine monitoring, and I think many of
9 these people who manage to return to successful practice
10 have not turned to alcohol.
11 Most importantly, though, is that no
12 information was provided on the incidence of urines
13 positive for any comparator drug, and without this
14 comparison, it's really difficult to assess whether 10
15 percent is high, low, or somewhere in between. So, I look
16 forward to seeing that data in the final study report as
17 well.
18 DR. STRAIN: Thank you, Dr. Winchell.
19 At this point I think that we'll go ahead and
20 take a 15-minute break and resume here at 20 till 3
21 o'clock.
22 (Recess.)
23 DR. STRAIN: Next we'll be hearing from Janet
24 Greenblatt on the DAWN data.
25 MS. GREENBLATT: Today I'm going to be

1 presenting some data on tramadol, but I'm also going to be
2 telling you a little bit about how our DAWN data are
3 collected and try to put it in context.
4 In the early 1970s, DAWN was begun by the Drug
5 Enforcement Administration. They selected a sample of
6 hospital emergency departments and began collecting data on
7 them. The data were never weighted to become a
8 representative sample for the nation. And over the years,
9 hospitals closed, they merged, there were voluntary
10 terminations, and the sample was never updated. So,
11 through attrition and nonrandom sampling, it became a
12 sample that was no longer valid. During that period our
13 reports were produced and numbers were given out. However,
14 in many cases you couldn't compare the numbers from year to
15 year, and it was unclear what exactly it meant.
16 So, in 1988 a new sample was drawn from the
17 American Hospital Association files which contain about
18 5,000 hospitals. The sample today consists of about 640
19 hospitals with about 500 responding. We select a very
20 large sample of hospitals in 21 metropolitan areas. In
21 fact, in five cities all the samples are selected. That's
22 Baltimore, Buffalo, Denver, San Diego, and San Francisco.
23 It's important to note that these are episodes,
24 not people that are counted. One person can make more than
25 one visit. We don't have names on the files, so we have no

1 way of differentiating that they're unique people.
2 People also get a little confused with the
3 terminology, episode, visit, and mention. An episode is a
4 visit to a hospital emergency department by a person.
5 During that visit, they may mention more than one drug.
6 They can mention up to four drugs per episode. So, we have
7 many more mentions than we have episodes.
8 We actually hire reporters who abstract records
9 from the medical records in the hospital emergency
10 departments. These are usually a member of the ED
11 themselves, or when we can't recruit somebody from the ED,
12 we go outside and bring in somebody to abstract the
13 records. The staff are trained and they're reviewed, and
14 we have quality control procedures in all the hospitals.
15 But the abstracting is only as good as the
16 records, and the record consists of what the person reports
17 to the doctor or nurse, whoever is filling it out. It's
18 very rare that a toxicological report would be included in
19 the records because even if the person is admitted to the
20 hospital, the report would follow them to the hospital part
21 and would never enter into their emergency department
22 record. So, what we rely on are self-reports and doctor
23 observations.
24 It's important to note also that DAWN measures
25 the health consequences of drug use and not the prevalence

1 of drug use. The people who come into the hospital EDs are
2 sick. They're people who have taken overdoses. They've
3 used drugs improperly, and in no way does this measure how
4 many people in the United States are taking any particular
5 drug.
6 We do feel that the measures are important,
7 though, because they measure the adverse effects of people
8 using drugs improperly. In this system we generally
9 measure the people who are the hard core users, people who
10 have gotten into trouble with their drug use. In fact,
11 over time we've seen that our reports to DAWN -- the
12 episodes -- the people are getting older and older,
13 evidencing their long-term drug use and the health effects
14 of those drugs.
15 Now, to be eligible as a DAWN case, the patient
16 has to be treated at the hospital ED, and the patient's
17 presenting problem must be induced or related to a drug
18 overdose or a drug problem.
19 Now, it has to be the patient themselves, and
20 their problem has to be related to their own drug use. We
21 have people who come in from car accidents who were in the
22 accident because they've been using drugs, and they're
23 considered a DAWN case. However, somebody who was riding
24 in the car who was also using drugs -- the accident was not
25 a result of their own drug use, so they wouldn't be counted

1 as a case. It gets very complicated and very murky in some
2 cases.
3 The case has to involve the nonmedical use of a
4 legal drug or any use of an illegal drug, and I'll just
5 talk about the nonmedical use of a legal drug since that's
6 what we're primarily interested in today.
7 People use the drugs without a prescription or
8 they use the drugs with a prescription improperly. They
9 can take more of them than were prescribed. If it's
10 prescribed for 4-hour doses, they could take it within 3
11 hours. They're not using the drug as it was prescribed for
12 them, or they're using it without a prescription.
13 And the reason for taking the drug is a suicide
14 attempt or gesture, they're dependent on the drug, or a
15 psychic effect. I wanted to go into a little detail about
16 what a psychic effect means.
17 Psychic effect are two cases which is
18 recreational use to get high or using the drug for kicks.
19 We get a lot of recreational use of cocaine and heroin and
20 drugs like that.
21 Other psychic effects are to improve or enhance
22 any mental, emotional, or physical state. This may be
23 depression, anxiety, to relieve a headache, to reduce pain,
24 to stay awake, to relax, to get to sleep. But the critical
25 point is that they're not taking this drug to reduce pain

1 in the way that it was prescribed. They're taking it
2 either too much or too often or they don't have a
3 prescription.
4 Now, our form is very simple. It's just one
5 page. As I mentioned before, you can record up to four
6 drugs per episode. We get very basic information on
7 demographic characteristics, age, race, ethnicity, and
8 gender.
9 One interesting thing that we've just recently
10 been thinking of doing a study on is the home ZIP code to
11 find out where the people live who are coming to the
12 hospital emergency rooms, if they come within their ZIP
13 code or from someplace else.
14 Now, there are two interesting fields on the
15 form, the reason for taking the substance and the reason
16 for the present contact. Unfortunately, this refers to the
17 episode, not a particular drug. There is only one reason
18 given for taking the substance, and this could refer to any
19 of the four drugs that are on the form. Also, the reason
20 for the present contact is -- you know, I came in with an
21 overdose, but I took aspirin. It may refer to the aspirin
22 or it may also refer to the codeine that they took. So,
23 that's one problem with the form.
24 We have the disposition, whether they're
25 released or admitted.

1 We only collect alcohol information if alcohol
2 was involved with a drug, so we don't get alcohol alone.
3 We just get alcohol involvement with drugs.
4 The forum in which the drug was acquired.
5 That's one of our worst data fields. We rarely get good
6 information on that.
7 The route of administration. That's another
8 difficult one to get, although we do have fairly good
9 information on that, whether it's oral or injected.
10 And the source of the substance, whether it's a
11 street buy or whether they bought it over the counter. We
12 don't get very good information on that.
13 We also have a little write-in part to know
14 whether it's an HIV or AIDS patient. This has, as you can
15 imagine, grown considerably over the past years, and in our
16 reports, we don't include the HIV/AIDS patients because
17 generally the reason that they're coming to the hospital
18 emergency room may have something to do with their drug
19 use, but it's because they have AIDS and they're being
20 treated for all the health consequences of AIDS.
21 Now, I wanted to give you a little sample
22 information because it's very germane to this talk. In the
23 21 metropolitan areas, there are 837 total hospitals, and
24 of those we have selected 526. So, in those 21
25 metropolitan areas, you can see that we have a very sizable

1 sample. 405, almost half of all the eligible hospitals,
2 respond to the survey. That makes their average sample
3 weight, the weight that we have to apply to each episode,
4 between 1 and 4. In those cities I told you about where we
5 take all the hospitals, their rate is just very close to 1,
6 and most of the weights are close to 1.
7 Now, the national panel consists of all the
8 other hospitals in the country. There are 4,100 of them.
9 We selected a sample of 113 of those 4,100 hospitals in the
10 rest of the country. Only 83 of them respond. So, those
11 national panel hospitals have quite a sizable weight, which
12 can be 46 to 76 that is applied to each estimate.
13 The reason this was done is primarily because
14 DAWN was established to keep track of drugs like cocaine
15 and heroin, and those exist mainly in the large inner
16 cities. So, that's why the 21 cities were oversampled and
17 why they continue to have the emphasis of the sample.
18 Now, the impact of this is that in terms of the
19 tramadol episodes that we found, there were 117 unweighted
20 episodes in the 21 metropolitan areas, and 27 that we found
21 in the national panel. Those 27 in the national panel,
22 after applying that rather large weight, came to equal 993
23 which was about two-thirds of all the estimates of tramadol
24 that we found. Whereas, in the metropolitan areas, the
25 117, after they were weighted, became 209. So, it was just

1 about doubled. You can see that any episodes that we find
2 in those national panel hospitals can have a very large
3 impact on the estimates.
4 Now, we did find cases in every single one of
5 the 21 metropolitan areas, and in the national panel there
6 were 7 in the northeast, 3 in the north central area, 16 in
7 the south, and 1 case in the west. So, from the national
8 panel cases, most of them were in the south.
9 Now I'm going to present the Ultram data. We
10 did not find any cases on anyone under the age of 18. On
11 the left you'll see the 1995 data and on the right the 1996
12 data. The estimates doubled from 660 to 1,200. Now, of
13 course, Ultram was only introduced in 1995.
14 There was a doubling among males and a doubling
15 among females, pretty much proportionate. So, it's still a
16 drug that's primarily in the females.
17 This is the percent all. You can see that from
18 1995 to 1996, it's about 60 percent female and around 40
19 percent male, and there was no change.
20 Most of the cases are in the 35 and older age
21 group, and that went up from 1995. In 1995 there were 53
22 percent of the cases, and in 1996 it was 60 percent of the
23 cases among the 35 and older age group. There was also a
24 very small increase in the 18 to 24 age group.
25 Almost all the cases are among whites, 76

1 percent in 1995 and 87 percent in 1996. Even the
2 percentage of black and Hispanic cases among blacks and
3 Hispanics has gone down in 1996.
4 This is the variable I was describing to you,
5 motive for taking the drug, which, as I said, applies only
6 to the episode, not the particular drug. However, I looked
7 at this for the cases that were tramadol only and I'll
8 mention that after this.
9 In 1995, 75 percent of the cases were suicide,
10 the green bar. By 1996, it had gone down to 57 percent of
11 the cases. The field of other psychic effects went from 10
12 percent in 1995 to 30 percent in 1996. That's the red bar.
13 As you may recall, the other psychic effect
14 would be somebody saying that they took the drug to enhance
15 or improve any physical condition, mental or emotional
16 state. They might have said something to reduce pain.
17 Looking at the distribution for males and
18 females, females were more likely to state other psychic
19 effects, 22 percent for males -- this is 1996 -- and 37
20 percent for females. Males were more likely to say suicide
21 attempt or gesture than females, which is unusual since
22 most of our cases of suicide are female, a great
23 proportion.
24 Now, just looking at dependence, other psychic
25 effects, and suicide, these are the cases of Ultram. 64

1 percent overall were suicide and 34 percent were other
2 psychic effects. I am going to compare this with some
3 other drugs that have been mentioned here today already.
4 Codeine, we have 30 percent for dependence.
5 There are no dependence for tramadol. D-propoxyphene, 9
6 percent dependence, and oxycodone, 52 percent dependence.
7 Daypro, there are no dependence. Now, these are people who
8 gave this as the motive for taking the drug.
9 The tramadol is most similar to the
10 d-propoxyphene, with 59 percent saying suicide and 15
11 percent other psychic effects. I'll go back to that other
12 slide so you can see again. 64 percent suicide, 34 percent
13 other psychic effects. So, it's most like the
14 d-propoxyphene.
15 Now, in 1995, 67 percent of the cases involving
16 tramadol were only tramadol, no other drug. In 1996, it
17 was 63 percent, very close. Of those cases that involved
18 only tramadol, 60 percent said other psychic effects and 37
19 percent reported suicide. So, predominantly the reason
20 given was other psychic effects.
21 That concludes my presentation.
22 DR. STRAIN: Thank you.
23 Finally, we'll hear from Dr. Alderfer with the
24 review of the FDA's Medwatch reports.
25 DR. ALDERFER: Again, I'm Ray Alderfer with the

1 Division of Pharmacovigilance and Epidemiology, and I'll be
2 discussing FDA's spontaneous reports for
3 abuse/dependence/withdrawal syndrome and also be making
4 some comments on the sponsor's proactive surveillance
5 program.
6 On April 10th of this year, a pharmacist from
7 Troy, New York called the FDA inquiring about the agency's
8 data on dependence reported for tramadol. An orthopedic
9 surgeon asked her for information about tramadol-related
10 dependence. He had noted drug-seeking behavior among his
11 patients on tramadol, and he himself had experienced
12 dependence after a short course of tramadol taken for
13 shoulder pain.
14 Both the physician and the pharmacist were
15 concerned that tramadol is being marketed as a nonopioid
16 analgesic and that tramadol's unscheduled labeling gives
17 physicians a message that this is not an opioid. Other
18 pharmacists at the reporter's hospital shared these
19 concerns.
20 Before moving on to talk about the reports of
21 dependence, withdrawal syndrome, and abuse, I'll make a few
22 comments about FDA's spontaneous reporting system. We call
23 this the SRS.
24 It's a database of adverse drug events which
25 are reported by sponsors, health professionals, and

1 consumers. Each report is coded by drug as well as by
2 COSTART terms which capture the adverse events. These can
3 be up to four COSTART terms per report.
4 We then enter selected data points into an
5 electronic database, and this has been searchable since
6 1969.
7 Dr. Jones has already covered some of the
8 limitations of this database. For one thing, we will get
9 duplicate reports when there are direct reports coming in
10 in addition to those sent in by sponsors. We do not
11 determine causality. There's difficulty in trying to use
12 this for incidence rates. It's not very good for comparing
13 adverse event rates across different drugs because of
14 differences in trends in reporting, differences in the
15 marketing cycle of the drug, and a number of other reasons.
16 Additionally, the agency is now in the process
17 of converting to our adverse event reporting system, which
18 we refer to as AERS, and all data coming in to the agency
19 is now going into the AERS system as of the 1st of November
20 1997. So, reports that I'll be presenting on today
21 basically were searched in the first week of February of
22 1998, and that covers reports which were received by the
23 agency about through August of 1997.
24 A total of 2,882 reports for all different
25 adverse events have been received by the FDA as of the

1 search which was done February of 1998. Again, this
2 reflects reports which had been received sometime by August
3 of 1997. Of those, 736 were serious and there were 91
4 deaths.
5 Also on this slide, we see the COSTART terms
6 listed for the 2,882 cases, and we note that convulsions,
7 withdrawal syndrome, and drug dependence are among the more
8 frequently noted COSTART terms.
9 We don't have a specific term in the SRS for
10 abuse, so what we did is we searched by a collection of
11 COSTART terms, including drug dependence, drug dependence
12 addiction, withdrawal syndrome, or tolerance increase.
13 This was expected to capture those cases which would
14 involve abuse. In each of these cases, tramadol was listed
15 as a suspect drug, and we got a total of 452 reports of
16 what we called dependence by this search. Of this 452, 57
17 were serious, and there were 4 foreign reports.
18 I might say that the criteria for serious here
19 is hospitalization, death, congenital anomaly, or
20 disability.
21 Here we see the most frequent COSTART terms
22 reported for the 452 reports of dependence: withdrawal
23 syndrome, drug dependence, and drug dependence addiction
24 would be expected to be the highest, as they are. We also
25 note that 41 counts of euphoria showed up. Tolerance

1 increase came in with 25, but of those, only 2 were
2 tolerance increase without one of the top three there,
3 withdrawal syndrome, drug dependence, or drug dependence
4 addiction.
5 Of 452 reports of dependence, tramadol was the
6 only listed drug for about two-thirds, or 309. Of the
7 rest, one or more drugs were listed as either suspect or
8 concomitant.
9 We have only 9 counts of other drugs with abuse
10 potential listed as suspect for this 452 reports. These
11 included propoxyphene, hydrocodone, codeine,
12 dextromethorphan, and methadone.
13 Here we see the drugs with abuse potential
14 which were used concomitantly with tramadol for these 452
15 reports of dependence. This list is listed here, codeine,
16 cannabis, cocaine, fentanyl, hydrocodone, meperidine,
17 methadone, oxycodone, pentazocine, and propoxyphene.
18 I think from these two slides we see that for
19 the 452 reports, tramadol was the primary suspect drug.
20 Now, we reviewed 174 cases of dependence.
21 You'll recall we searched by the collection of COSTART
22 terms and got what we defined as dependence. Now we went
23 in and looked at all 57 serious cases, as well as a 30
24 percent sample of the remaining 395 nonserious cases. We
25 abstracted data from that 174, including tramadol dose and

1 duration of treatment, an assessment of whether abuse was
2 involved in that report, history of opiate or other
3 substance abuse, and whether the report was coming through
4 the independent steering committee or coming through normal
5 spontaneous reporting mechanism routes.
6 Here we defined abuse as whether the reporter
7 thought there was abuse occurring, whether or not there was
8 drug-seeking behavior, or whether or not there was pursuit
9 and experience of euphoria.
10 This case illustrates a case where we thought
11 there was evidence of abuse. A 25-year-old female with a
12 history of narcotic abuse developed drug-seeking behavior
13 while being treated with tramadol for chronic
14 endometriosis. Before starting tramadol, she had been in
15 recovery for three years. She began craving tramadol,
16 obtaining prescriptions from several physicians, and taking
17 several tramadol tablets at a time to get high.
18 Realizing her abuse, she stopped tramadol and
19 experienced nausea, vomiting, diarrhea, shakes, headaches
20 over the following three days. She began attending
21 Narcotics Anonymous meetings daily and switched to an NSAID
22 to control her pain.
23 This is a verbatim description taken from the
24 report.
25 Here's another verbatim from a case report. A

1 35-year-old male, taking tramadol for chronic back pain
2 over four to five months, developed tolerance and increased
3 his dose to 600 milligrams per day. On two occasions, this
4 patient ran out of tramadol and developed withdrawal
5 symptoms 36 hours after stopping the first time and 18
6 hours after stopping tramadol the second time. His
7 symptoms included anxiety, muscle tingling, sweating, night
8 sweats, chills, nausea, vomiting, visual hallucinations,
9 and a weird feeling in his chest. He had a history of
10 abusing Darvocet and Lortab, but the reporter did not feel
11 that the patient was exhibiting drug-seeking behavior.
12 Of the 452 cases of what we defined as
13 dependence, 57 were serious. Of these, there were 49
14 hospitalizations. 39 of that 49 involved treatment for
15 addiction. There were 2 life-threatening cases. Both of
16 these involved seizures. There were 6 deaths. 1 was with
17 drowning status post a seizure. There was 1 overdose, and
18 4 were not obviously attributable to tramadol.
19 The dose of tramadol was available for 92 out
20 of the 174 cases. We can see here that in 63 percent of
21 cases the dose was within the labeled amount, and in the
22 other 37 percent the dose ranged from 500 to 1,500
23 milligrams per day.
24 In this slide we looked at the dose of tramadol
25 by a history of reported abuse, and the patients who had a

1 history of reported abuse were taking significantly more
2 than those who did not report abuse. Those with a history
3 of reported abuse were about -- I think the total there was
4 -- anyway, there was a significantly larger portion of
5 patients with a history of reported abuse who were taking
6 greater than the labeled amount.
7 Here we see the duration of treatment for
8 tramadol, which was available for actually 88 cases.
9 That's a mistake on this slide. About 16 percent had been
10 taking tramadol for 1 month or less, 41 percent for 2 to 5
11 months, 28 percent for 6 to 11 months, and approximately 15
12 percent for 12 to 18 months.
13 Here we have the proportion of dependence cases
14 involving abuse by the source of the report. For
15 spontaneous reports, about 41 percent involved abuse,
16 whereas those coming from the independent steering
17 committee about 90 percent involved a determination of
18 abuse.
19 This shows the proportion of dependence cases
20 involving a history of opiate abuse by the report's source.
21 About 84 percent of those coming from the sponsor's
22 steering committee involved patients with a history of
23 opiate abuse, whereas about 36 percent of normal
24 spontaneous reports involved the reported history of opiate
25 abuse.

1 We generally have trouble trying to make
2 comparisons between drugs and our spontaneous reporting
3 system. Any method we use has problems, as Dr. Jones has
4 described. So, we didn't think it was appropriate to try
5 to compare reporting rates between tramadol and other
6 analgesics. So, we thought maybe a better way of looking
7 at sort of a snapshot, if you will, of what the pattern was
8 comparing tramadol to other analgesics would involve the
9 proportion of total reports which were dependence reports.
10 We subtracted out 71 reports for tramadol,
11 assuming that about 16 percent of what we defined as
12 dependence here was coming from the independent steering
13 committee. So, that left about 381 reports of dependence
14 on tramadol out of a total of 2,182 which would give a
15 proportion of abuse reports at about 13 percent. For
16 propoxyphene, we have a little under 12 percent; oxycodone
17 at about 7.1 percent; hydrocodone, 5.3 percent; codeine,
18 about 4 percent. We put in here Daypro, an NSAID approved
19 in 1992. It had a total of 4 dependence reports, and that
20 is much less than 1 percent.
21 Another way of looking at tramadol's abuse
22 potential or its problem with dependence, withdrawal
23 syndrome, and abuse in our spontaneous reporting system is
24 to compare it to the COSTART profile for other analgesics.
25 Here we show tramadol with its COSTART terms compared to

1 propoxyphene. For both of these drugs withdrawal syndrome,
2 drug dependence, and drug dependence addiction are among
3 the most frequently reported COSTART terms.
4 A similar pattern is also shown for oxycodone
5 with drug dependence addiction, drug dependence, and
6 withdrawal syndrome among the more frequently reported
7 COSTART terms.
8 In this slide, we have graphed the reports
9 coming into the agency. In the bottom curve here, we have
10 the reports by the reported date of reaction, which for
11 many reports was missing. So, if the reported date of
12 reaction was missing, we graphed the date received by the
13 agency and we also had the total combining these bottom two
14 curves and the top curve. This, of course, is by quarter,
15 since 1995 through the last quarter of 1997.
16 However, for the third quarter of 1997, our
17 database is incomplete. As I pointed out before, we're
18 still entering in reports of labeled events in the third
19 quarter. So, this should not be taken as a complete data
20 point.
21 I think what we see here is evidence of the
22 media attention and the Dear Doctor letter which would
23 probably account for some of the rise here in 1996. This
24 is frequently seen whenever we send out a Dear Doctor
25 letter. We continue to have reports of withdrawal

1 syndrome, dependence, and abuse coming into the agency.
2 We put this in the perspective of the marketing
3 data, and this is the National Prescription Audit new
4 prescriptions for 1995, 1996, and 1997. There was an
5 increase from 1995 to 1996, and then from 1996 to 1997, the
6 marketing has been relatively flat.
7 We draw the following conclusions from our
8 review of the spontaneous reporting system. Reports of
9 dependence, addiction, and withdrawal syndrome are numerous
10 for tramadol. Approximately half of these involved abuse.
11 More than 60 percent of dependence-related reports involved
12 daily doses of 400 milligrams or less. Reports from the
13 independent steering committee were more likely to involve
14 abuse and patients with a history of abuse. Spontaneous
15 reports typically involve tramadol used for analgesia at
16 the labeled doses. And finally, tramadol is similar to
17 other opioids in its profile for dependence-related
18 reports.
19 I move on now to a review of the progress
20 report of the independent steering committee. Dr. Winchell
21 has reviewed the impaired physicians program, and the
22 sponsor did not supply any data on the pain population.
23 So, my comments will be directed to what they call the
24 proactive surveillance program.
25 As we've already heard, tramadol was marketed

1 unscheduled by the decision of the agency and the Drug
2 Abuse Advisory Committee in 1994, but the advisory
3 committee was asked for a special surveillance program and
4 the sponsor's steering committee was created to detect
5 early abuse, to intervene when abuse was found, and also to
6 recommend scheduling, if such was needed.
7 The proactive surveillance program, as we've
8 heard before, involved NIDA grantees, as well as other drug
9 experts. A quarterly questionnaire was sent out to all
10 these key informants. I think this has been relatively
11 well covered.
12 I might make some more comments about the use
13 of the DSM-IV criteria for abuse. We also note that abuse
14 rates were calculated using IMS data in a derived number of
15 patients.
16 You've already heard about the results of the
17 proactive surveillance. I won't spend any time on that.
18 This is just to remind you that a number of
19 cases of abuse had been found through the activities of the
20 key informants. In Atlanta there were physicians who were
21 readmitted for treatment of abuse, and I think it was in
22 Phoenix there was a physician who was unaware of abuse
23 potential of tramadol and was treating opiate abusers with
24 tramadol. We've already heard about this from Dr. Cicero.
25 So, finally, our comments on the proactive

1 surveillance system. We feel like tramadol abuse has been
2 detected by the activities of the sponsor's steering
3 committee.
4 The Dear Doctor letter in 1996 would account
5 for some of the rise in reports which came in in 1996. So,
6 some of that decline is probably related both to the
7 aftermath following the Dear Doctor letter, as well as
8 perhaps some decrease in reporting of time.
9 We want to emphasize that reporting rates are
10 not incidence rates. What we have with the reporting rates
11 created by the independent steering committee is a
12 numerator which consists both of spontaneous reports coming
13 in to the normal Medwatch or normal sponsor mechanisms, as
14 well as reports which are solicited by the key informants.
15 The key informants, while they target a high risk
16 population, there really is no sampling scheme by which to
17 project those numbers to a nationwide sample. As we know,
18 spontaneous reports suffer from under-reporting. It's
19 often thought that for nonserious reports -- and this would
20 fall into a category of nonserious reports -- the reporting
21 rate is probably less than 10 percent of all events
22 happening.
23 Finally, we have some questions about the use
24 of DSM-IV criteria for abuse in a surveillance system for
25 spontaneous reports. Frequently reporters are not giving

1 complete data. They're not intending to have their report
2 evaluated by such strict criteria, and it may not be
3 appropriate to use DSM-IV criteria in this kind of a
4 surveillance system.
5 The nationwide denominator probably does a
6 pretty good job of capturing the population at risk for
7 tramadol abuse, but the problem is with the numerator. We
8 really don't have all the reports captured.
9 So, we conclude that we can't make a conclusion
10 that the abuse rate is low for two reasons.
11 First, there's really not a true incidence rate
12 so that to talk about a low rate of abuse in a risk-benefit
13 balance is really problematic.
14 Secondly, there really is no comparator.
15 There's no context for saying that abuse is low.
16 And that concludes my remarks.
17 DR. STRAIN: Thank you, Dr. Alderfer.
18 I would now like to move to the discussion
19 period of the committee where the committee can pose
20 questions to the FDA, to the sponsor. I would remind the
21 committee that our ultimate goal is to respond to the three
22 questions that have been posed to us so that as time
23 progresses over the remainder of the afternoon, I'll start
24 to focus us in on that.
25 I realize that there is a desire at times for

1 the FDA to pose questions to the sponsor or the sponsor to
2 pose questions to the FDA. I'm going to suggest that not
3 just literally but figuratively as well and operationally
4 the committee place itself between the FDA and the sponsor.
5 (Laughter.)
6 DR. STRAIN: The proverbial rock and a hard
7 place and that questions will come from the committee to
8 the sponsor and dialogue between us and dialogue with the
9 FDA.
10 Dr. Simpson.
11 DR. SIMPSON: I just wanted to clarify how the
12 DAWN cases were elicited, first of all. I looked at the
13 form and it looks as if -- for example, the reports on what
14 drugs they took were either self-report or could be
15 confirmed by toxicology. Is that right?
16 MS. GREENBLATT: They could be. However, they
17 rarely are.
18 DR. SIMPSON: The reason you might not,
19 therefore, have children is typically -- this is just what
20 I've heard anyway -- parents were unlikely to report that
21 their child took certain drugs and the children also are
22 likely to. Is that true?
23 MS. GREENBLATT: I wouldn't know about that.
24 We do collect data on patients from the age of 6 on up, and
25 I really wouldn't know if they're less likely to report

1 that.

2 DR. SIMPSON: I was just involved in -- and the

3 problem was that they weren't told at the beginning that

4 the children had taken various drugs.

5 MS. GREENBLATT: Yes, could be.

6 DR. STRAIN: Dr. de Wit?

7 DR. de WIT: I have a question for Dr.

8 Greenblatt. I was disappointed in your presentation of the

9 data that you didn't really compare the number of reports

10 with this drug to other drugs. On one of your final slides

11 there, you have some numbers for codeine, propoxyphene,

12 Daypro, and oxycodone. You didn't say anything about that

13 and you didn't tell us what the comparator number for

14 tramadol would be. Could you comment?

15 MS. GREENBLATT: The number for tramadol is on

16 the earlier slides, but it's 1,202 for 1996, and those are

17 the 1996 figures, the n's on the other slides. But those

18 are the number of episodes on the last slide.

19 DR. de WIT: And the reporting period for --

20 oh, it's for 1996. It's just for 1996. Is that right?

21 MS. GREENBLATT: Right. For 1996,

22 d-propoxyphene was 6,449 reports. Codeine was 1,198

23 reports. Daypro, 761 episodes, and oxycodone was 2,755.

24 DR. de WIT: So, based on these numbers, where

25 would you say that tramadol falls?

1 MS. GREENBLATT: I believe it's in the top 100
2 drugs reported to DAWN. It's close to in the 60's. I
3 don't have the table with me that I could look that up, but
4 it is in the top 100 drugs.
5 Tramadol in 1996 was 1,202. So, it's a little
6 more than codeine, a lot less than d-propoxyphene. 1,202
7 was the total number.
8 DR. de WIT: And this codeine is just one
9 formulation of codeine?
10 MS. GREENBLATT: Yes. Hydrocodone is another
11 field.
12 DR. de WIT: I see, okay.
13 DR. STRAIN: Other questions?
14 Dr. Klein, I'd like to ask, without an adequate
15 comparator drug, without a similar system that could be
16 used over a similar time period for comparison -- so, some
17 of the things from the DAWN data may represent looking at
18 the percentage of dependence reports out of all the reports
19 -- I mean out of the adverse events reports, not DAWN.
20 There we're confounded by the time period that a drug has
21 been available. There are similar difficulties, it seems
22 like, with the different ways that the different ways that
23 the FDA has attempted to look at the data.
24 I then fall back to Dr. Cicero's independent
25 steering committee time by quarter effect showing a rise up

1 to the first half of 1996, but then a falling off in the
2 rates of report. And assuming a relatively consistent
3 mechanism operating over time for reports to occur, that
4 would seem rather persuasive that there's not an increase
5 going on in abuse of tramadol. I've never felt that I've
6 gotten a sense back as to how the FDA responds to that
7 comment.
8 Have I adequately expressed the question or
9 have I --
10 DR. KLEIN: Well, I don't know. We'll see what
11 the answer comes out.
12 (Laughter.)
13 DR. KLEIN: We recognize the fact that there is
14 a problem with an old drug versus a new drug. You're not
15 going to have the same level of reporting for a drug that's
16 known, that's recognized, that has a long history. I
17 should preface this by saying this point should be
18 addressed by our Epidemiology Division. But it's my
19 opinion that you just will not have the same level of
20 reporting for an old drug.
21 Now, oxaprozin was used as a comparator because
22 it was approved in the 1990s as a nonsteroidal anti-
23 inflammatory. So, we felt that that would help provide
24 some balance at least on the time picture for these
25 dependence and abuse type of reports in this more recent

1 era. So, that compares on one level, although it's
2 pharmacologically different from tramadol.
3 DR. STRAIN: Let me try rephrasing the
4 question. If you accept that the independent steering
5 committee is operating under the same mechanism over time,
6 that things haven't changed over time in its two- to three-
7 year operation, would you be reassured that the curve is
8 drifting downwards?
9 DR. KLEIN: No, I'm not reassured.
10 DR. STRAIN: And why not?
11 DR. KLEIN: As Dr. Alderfer stated, data is
12 still being entered from the third quarter of 1997. We see
13 a slight decline from the previous quarter, from the second
14 quarter of 1997, in these reports, but it's not complete.
15 DR. STRAIN: I guess I was referring to the
16 independent steering committee's figure showing time
17 effects, not the one from the adverse effects reports. But
18 regardless, you're not reassured by that.
19 Dr. Alderfer, were you going to --
20 DR. ALDERFER: Yes. I think one point we
21 should make here is that the reports coming from the key
22 informants are for a very small segment of the population.
23 I think we're concerned about abuse which is happening out
24 there in the population which isn't being covered by the
25 key informants.

1 Again, I think we have a lot of data still to
2 enter to see whether a trend is really downward yet. We
3 feel like, even given the number of reports we're seeing,
4 it's still a substantial amount of abuse going on.
5 DR. STRAIN: I may come back to this, but Dr.
6 Simpson.
7 DR. SIMPSON: If you want to continue with
8 yours, and then I'll ask mine.
9 DR. STRAIN: I guess I would be curious then to
10 know is there an acceptable level of abuse that the FDA
11 would have?
12 DR. McCORMICK: I think really again, to bring
13 us back to our discussion from early this morning, the
14 Controlled Substances Act really asks us to look at abuse
15 in the context of other drugs. Again, it's a relative
16 thing.
17 One of the problems that we've seen with some
18 of the data sets is that we see a slope over time, but
19 we've no comparators. So, we need to look at those data
20 sets where we do have comparators.
21 Again, we have a ceiling and a floor and we
22 know what those are. Again, our query to you is to help us
23 put this drug in the context of that ceiling and floor or
24 completely outside of the room, if you will, because the
25 boundaries have already been established.

1 DR. STRAIN: To take it another step, as we've
2 been talking about this, in the methadone clinic that I
3 work in we will get patients showing up with a urine
4 positive for amitriptyline, and I'm sure Dr. Khuri, Dr.
5 Andorn probably have had this happen as well. The general
6 clinical lore is that these are patients who are using
7 amitriptyline because of its strong anticholinergic effect.
8 As we also have talked about and has been eloquently stated
9 by several of the sponsors, tricyclic antidepressants can
10 result in a withdrawal syndrome. So, while I typically
11 don't tell my patients that I place on Elavil that this is
12 an abusable drug, in actuality there is a small but regular
13 proportion of patients who use amitriptyline, abuse it, are
14 not using it by prescription, and could be considered
15 physically dependent on it given the clinical literature of
16 a mild withdrawal syndrome.
17 Should amitriptyline be scheduled given that?
18 DR. McCORMICK: Fortunately, that's not
19 something we have to decide today.
20 DR. STRAIN: Well, I guess it comes back to you
21 want a comparator and --
22 DR. McCORMICK: I guess the comparators that we
23 look at are the drugs that have gone through this process,
24 that have gone through the evaluation, drugs that have a
25 similar pharmacology. We have those comparators. Maybe

1 they're not the best comparators. Maybe there were
2 mistakes made over time, but they're the ones that we have
3 to deal with.
4 DR. STRAIN: As I understand it, tramadol's
5 analgesic effects are blocked by naloxone. Correct me if
6 I'm wrong on this, but about 30 percent or so of the
7 analgesic effect.
8 DR. YOUNG: That appears to depend on the
9 assay.
10 DR. STRAIN: So, just to follow through with
11 this, a substantial proportion of its effects are thought
12 to be mediated by catecholamine reuptake blockade.
13 Correct? Possibly? Which would be the mechanism of
14 amitriptyline. Right? We could continue this logic.
15 I struggle with this and I don't have an
16 answer. I'm seeking the FDA's position on this where
17 things fall.
18 DR. BRASE: When it comes to blockade of
19 uptake, tricyclics like imipramine and amitriptyline are an
20 order to two orders of magnitude more potent than tramadol.
21 In reviewing the literature, I really am not very impressed
22 with that portion of the proposed dual mechanism of action.
23 When one blocks M1, like in the electrical
24 sural nerve stimulation test, there is a significant
25 decrease in the analgesic effect of tramadol, but there

1 still is a significant analgesic effect. But that effect
2 is no greater than what you could achieve in the same type
3 of study with acetaminophen, maybe like 23 percent increase
4 in threshold versus a 40 to 42 percent increase in
5 threshold.
6 I think there was either a tricyclic or an MAO
7 inhibitor that has been studied in that test and also that
8 drug, whether it was the MAOI or tricyclic -- I don't
9 remember which now -- had a level of analgesia about
10 comparable to that of acetaminophen. So, I think that's
11 the level of analgesia you're talking about, something for
12 maybe mild to moderate pain but not moderate to severe
13 pain.
14 DR. STRAIN: Thank you. I should let others
15 ask questions. Dr. Simpson, please.
16 DR. SIMPSON: I guess I wanted to come back to
17 some points that were raised right through.
18 It seems that the higher dose of tramadol does
19 have a possible attraction to people for dependence. If
20 you look at the studies, as Dr. Permutt showed, there were
21 some that seemed to like it, and then if you look at the
22 dose of tramadol, the 92 cases that Dr. Alderfer presented,
23 again you can see that for the higher doses there's a
24 tendency for dependence.
25 I guess the question then is what is the

1 likelihood of people to be up on those higher doses because
2 if that's true, then it's possible that the dependence rate
3 might increase. Is it?
4 DR. STRAIN: So, the question that you're
5 posing perhaps to the sponsor is what's the likelihood of
6 patients being treated with higher doses of tramadol?
7 DR. SIMPSON: Or having --
8 DR. STRAIN: Dr. Cicero?
9 DR. CICERO: Yes. I just want to respond.
10 Again, we've done those dose analyses and we still have 247
11 cases. The rate has been dropping over time. So, the
12 question you raise is, for the higher dose could in fact
13 some abuse occur? I think it is theoretically possible.
14 We've looked at that relationship and can't find one.
15 But will it increase over time? The answer
16 quite clearly at this point in time is no. It is
17 decreasing. So, we don't see anything coming on the
18 horizon or for the last 12 months that would suggest an
19 increasing rate at all.
20 DR. STRAIN: Does that answer your question,
21 Dr. Simpson?
22 DR. SIMPSON: I guess the question is, what is
23 the likelihood that you'd be picking up these cases?
24 DR. CICERO: I think, again, to the extent the
25 spontaneous reports would pick up on those events and our

1 key informant network, which consists not only of people
2 looking at drug abuse populations, but treatment clinics
3 and a somewhat wider population, to the extent they would
4 pick it up, I think it's quite likely we would pick it up.
5 DR. STRAIN: Dr. Khuri.
6 DR. KHURI: I previously had wanted to pursue
7 the same line of questioning that Dr. Strain had embarked
8 upon. Certainly in a drug abuse treatment center, you see
9 abuse of almost everything. Amitriptyline is certainly a
10 large one. There are many other substances.
11 I often judge abuse by the street value of a
12 drug, and a brownie of 50-milligram Elavil is much more
13 expensive on the streets of New York. Most of my patients
14 haven't heard of tramadol certainly. But I did notice in
15 the vast amount of literature that we read, there was a
16 street price quoted of tramadol in one of the papers which
17 was rather low. I was impressed at how low it was. But
18 then, of course, one man's or woman's euphoria is another's
19 dysphoria.
20 (Laughter.)
21 DR. STRAIN: Person.
22 DR. KHURI: I even have patients who enjoy
23 drinking on their Antabuse.
24 (Laughter.)
25 DR. STRAIN: So do I.

1 DR. CICERO: The price of tramadol on the
2 street in New Orleans was $1 which is actual cost of the
3 tablet. $2 to $5 is the maximum we've seen.
4 DR. STRAIN: Dr. Andorn?
5 DR. ANDORN: One of the questions I had -- and,
6 Dr. Cicero, you can probably answer it -- with high dose,
7 750-milligram IV bolus, of tramadol, is there a change in
8 the pharmacokinetics of the compound versus the chronic
9 dosing at 200, 400 per day?
10 DR. CICERO: I'm not sure about that. Someone
11 else would have to address it, but I do want to point out
12 we have exactly 6 cases of IV use of tramadol in the
13 country, all 6 of which reported that the drug was
14 extremely unfavorable by that route.
15 DR. ANDORN: That's not what I was asking. I
16 was asking about the studies that were done using 750-
17 milligram IV bolus and then comparing whether the patients
18 liked it compared to morphine or oxycodone, and that is
19 much higher than the daily dose recommended. But if
20 there's an alteration in the pharmacokinetics from bolus
21 dosing as compared to chronic dosing, we need to address
22 that.
23 DR. STRAIN: Dr. Jasinski, is that something
24 you -- there's a microphone right there, Don.
25 DR. JASINSKI: I don't think that data exists.

1 The only data we have is this study which we're not
2 supposed to talk about -- okay, Cynthia -- which is this
3 last study. That was really to see if the M1 metabolite
4 was produced with the large oral doses.
5 Tramadol is a mystery. It's not a simply
6 classified drug. To try to make it simply as a prodrug
7 doesn't work. All we know is that if you look at that
8 data, the data we have, is if we give it orally in large
9 doses -- that was 400, which is 8 therapeutic doses --
10 acutely orally, we can produce the M1 metabolite. The
11 parent compound is about 1,000 nanograms. The metabolite
12 was a little less than 100 nanograms. That's the data and
13 we know that the Tmax, the time of maximum concentration,
14 is about the same and the half-lives are about the same.
15 That's the data that exist.
16 The question is if you gave this drug
17 chronically, would the metabolite accumulate? I don't
18 think so. There is a slight difference in the half-life.
19 DR. CICERO: We could answer both those
20 questions. There is in fact, I'm told, no saturation
21 kinetics with this drug and there is no induction of the
22 enzyme.
23 DR. JASINSKI: This makes the drug different
24 than propoxyphene and meperidine where the metabolites have
25 longer half-lives and accumulate.

1 DR. STRAIN: Thank you.

2 Other questions? Dr. McCormick.

3 DR. McCORMICK: I just would like to say a word

4 about the study that I have asked not to be spoken about.

5 This was a study that was completed I understand several

6 years ago and was submitted on Friday. We felt that 700

7 pages was inconsiderate of the advisory committee, and we

8 asked that they not be forced to look at it. We've not

9 seen it either.

10 DR. STRAIN: Thanks.

11 Yes, Dr. Cicero.

12 DR. CICERO: I do want to make a point. I

13 think Dr. Schnoll is not here, and I think I need to defend

14 him. He is one of the most superb clinical researchers in

15 this country. There was the suggestion, because we wrote

16 in our report a very brief summary of his study in a two-

17 sentence discussion of his results, that the study was in

18 some way flawed and had characteristics in it. I think

19 that's extremely unfair. On the record I think I will take

20 complete credit for that because most of that report was

21 drafted by me.

22 The deficiencies pointed out are indeed not

23 deficiencies. There will be a full report submitted. We

24 assumed that was proper procedure to submit a full report

25 and not to analyze some preliminary data. It is true 98

1 percent of the patients have been collected, but we
2 committed to the four states they would never reveal their
3 identity during the course of this particular study until
4 it is finished. That study is incomplete and to draw
5 criticisms of that report I think is very unfair to Dr.
6 Schnoll who is not here to defend himself. I just want
7 that to be in the record.
8 DR. STRAIN: Okay, thank you. It's in the
9 record. Thank you, Dr. Cicero.
10 Dr. Meyer.
11 DR. MEYER: Are there any other countries that
12 have scheduled this drug?
13 DR. STRAIN: Dr. Cicero?
14 DR. CICERO: No.
15 DR. STRAIN: Don't go away. Have any states
16 scheduled it?
17 DR. CICERO: To my knowledge, no.
18 DR. STRAIN: Other questions? Dr. de Wit?
19 DR. de WIT: Is there a discrepancy in the data
20 that the sponsor is presenting and the data that are
21 important to the FDA now with regard to the report? The
22 sponsor is reporting data on people who are actually
23 substance abusers, abuse and dependence. I believe Dr. --
24 DR. STRAIN: Alderfer.
25 DR. de WIT: Your point was that that reporting

1 system misses the most important component of abuse that
2 the FDA is concerned about over the last maybe two years
3 when the reports from the sponsor are going down. Is that
4 right?
5 DR. ALDERFER: I think what we're trying to say
6 here is that when the sponsor and the steering committee
7 talk about a rate of 1.5 cases of abuse per 100,000, that's
8 not really capturing all the abuse that's going on in the
9 U.S. That number is derived from a combination of
10 spontaneous reporting and a very small surveillance program
11 which is namely the key informants.
12 We just want to make clear that that's a
13 composite of reporting rate. First of all, there's no
14 comparison to any other drug, and it would be difficult to
15 have one in fact because this is an unscheduled drug.
16 Furthermore, the way that the sponsor is
17 defining abuse is a very strict criteria. We normally
18 don't apply DSM-IV criteria in a surveillance system like
19 this where you're getting spontaneous reports. The
20 reporters are not expecting to have the reports submitted
21 to DSM-IV criteria.
22 Furthermore, for normal spontaneous reporting,
23 there's going to be the effect of the Dear Doctor letter.
24 So, a lot of that big peak we saw in 1996 can be attributed
25 to the Dear Doctor letter. So, we probably haven't seen a

1 complete equilibrium for those reports coming in from the
2 normal spontaneous route.
3 Now, that Dear Doctor letter probably didn't
4 affect reports coming in from the key informants, but
5 remember that's a pretty small population, subset of the
6 population, that's being represented. Furthermore, there's
7 no way to project that to national population numbers.
8 That's not a systematic sample.
9 DR. de WIT: Did you see a decline in use in
10 your other indicators of abuse other than what the sponsor
11 has presented? In the period where there was a decline
12 after the Dear Doctor letter presumably, was there also a
13 corresponding decline in, say, DAWN reports or --
14 DR. ALDERFER: I can't comment on the DAWN
15 reports. For seizures, for example, we saw an increase in
16 reporting of seizures following the Dear Doctor letter, and
17 there has been some decrease following that.
18 DR. STRAIN: Would you identify yourself
19 please?
20 DR. GRAHAM: Yes. I'm David Graham. I'm a
21 scientific advisor in the Epidemiology Branch. I work with
22 Ray Alderfer. I just want to add a little bit to what he's
23 trying to describe in terms of some of our concerns.
24 The sponsor's independent steering committee --
25 their key informant system focuses -- if you think of a

1 study base. Where do the cases arise from as a study base?
2 The study base for the key informants is a very selective
3 population, a very selective population, a very small
4 proportion of, let's say, the total study base would be of
5 tramadol users. If you look at all tramadol use, I don't
6 know what the numbers are, but let's say for the sake of
7 argument, 95 percent of tramadol use is in people who don't
8 come from drug-abusing histories. 5 percent does. The
9 sponsor's study base focuses on that 5 percent. 95 percent
10 of the population is not under surveillance except by
11 spontaneous reporting. So, our concern is that conclusions
12 that one would make based on looking at trends in an
13 abusing population aren't necessarily what is happening in
14 the general population.
15 The opening slide in Dr. Alderfer's
16 presentation is an example of the type of thing we're
17 concerned about. A non-drug abusing citizen takes a drug
18 for a transient problem, shoulder pain, and determines
19 that, golly, I've become dependent on this drug. He's a
20 physician. I don't know what his definition of dependence
21 is, but he experienced various withdrawal symptoms when he
22 tried to take it and noted other symptomatology. Our
23 concern is that type of event represents abuse potential,
24 dependence potential, withdrawal potential, and there's no
25 handle on what the actual incidence rate for that would be.

1 Finally, people are concerned about our rates
2 going down over time. Dr. Alderfer has tried to explain
3 we're not talking about rates now. These aren't incidence
4 rates, and the sponsor's presentation of 1.5 per 100,000 is
5 not an incidence rate. But if you look at the various
6 figures that have been presented during the day, look at
7 that blip that occurred with the Dear Doctor letter in
8 1996, but look at the period before 1996 and the period
9 after 1996. They're fairly comparable. What you have to
10 view is that with spontaneous reporting of data, there is a
11 decline in the efficiency of reporting almost from day one.
12 So, reporting rates generally start off in the first year
13 being whatever they are and then they decline in successive
14 years. So, you've got a natural trend for reporting to
15 fall off with time.
16 It's compounded by the fact that the type of
17 reaction that we're talking about here and now doesn't land
18 you in a hospital usually or land you in the grave. So,
19 those are the type of things where you might get up to 10
20 percent reporting. But we're talking about things where
21 the reporting rates will be far less.
22 So, we're in a situation where we have signals,
23 just like the canary in the cave, that you see evidence of
24 a problem. You look at the reporting profile of the drug.
25 What Dr. Alderfer was trying to show there is that the

1 fingerprint of reporting for this product is very similar
2 to that of other opioids and distinctly different from
3 nonsteroidal anti-inflammatory drugs.
4 DR. STRAIN: Dr. Meyer and then Dr. McNicholas.
5 DR. MEYER: We're not going to get through
6 these four questions by 5 o'clock, and I want to push you
7 because I have to say that the problem, as a relative
8 newcomer to this committee, is an impressionistic one, but
9 it comes across as though we're revisiting 1994 more than
10 we are looking at post-1994 data. And on that I have to
11 fault the FDA. We have spent a huge amount of time dealing
12 with basic pharmacology that was reviewed in 1994. The
13 issue of what has happened since 1994 -- we haven't heard
14 the rest of the story.
15 We're also hearing I think a breakdown in the
16 level of discourse between the committee and the degree to
17 which the FDA trusts the process that has been set up. You
18 need comparative data, and I agree with Dr. Strain.
19 Without comparative data, you have no idea of being to --
20 the numerator may be unknown because we just don't have
21 enough information. So, you are flying, to some extent,
22 blind.
23 But what I'm hearing in terms of the urgency
24 is, to use Michael Klein's point that he made earlier,
25 leveling the playing field. This drug is -- and correct me

1 if I'm wrong -- so much like propoxyphene and maybe like
2 heroin and maybe like oxycodone, that these people have a
3 marketing advantage, and that's not correct in this
4 circumstance. You're left with the only vehicle you have
5 which is we didn't schedule this drug in 1994 and we are
6 responsible for that.
7 I think the committee in 1994 took a leap into
8 the unknown, but I think that you started a process and I
9 think you haven't finished the process. I think you
10 haven't really engaged with this committee -- you're
11 finding some of the data of concern to you, but you haven't
12 really sorted it out.
13 On the industry side, I'm concerned that all
14 the data are being presented against morphine. This drug
15 is not morphine. I think that if this committee were to
16 take a fresh look at this, this drug ought to be compared
17 -- and Don Jasinski must have some of this data somewhere,
18 not from his head but on slides -- how this drug stacks up
19 against the drugs that you're trying to compare it to,
20 propoxyphene and pentazocine and maybe oxycodone.
21 I disagree with Dr. Greenblatt. 2 percent is
22 not 9 percent in terms of your data. It's not the same as
23 propoxyphene. It's different in terms of the raw data that
24 you presented.
25 But I do think that there's a breakdown here

1 and you're bringing the committee in to deal with your
2 discomfort or somebody's discomfort, and we haven't heard
3 the rest of the story. I think we have to get this to play
4 out, and you have to be comfortable with the data you get,
5 and if you're not comfortable with it, then you have to
6 come back and say it's not good data.
7 But we're really being brought back to 1994 by
8 a lot of this material and inadequately I think by both
9 what industry presented, in terms of the comparator drugs,
10 and what you've presented in terms of basically stuff from
11 1991 and earlier.
12 So, I'm not comfortable revisiting many of your
13 questions because I think we're dealing with a marketing
14 issue and a precedent issue and a pharmacological
15 similarity issue that may or may not be there. But I do
16 think that we really have to get to those questions, and
17 I'm not sure how we do that.
18 DR. STRAIN: Dr. McCormick, do you want to
19 respond?
20 DR. McCORMICK: If I may. I guess I would take
21 issue with the fact that you feel that you've heard only
22 old data because we've made a tremendous effort to show you
23 only that information that has come to us since marketing.
24 Now, granted, some of the information that has come to us
25 since marketing should have come to us before marketing.

1 Nevertheless, what we have presented to you this afternoon
2 is new.
3 As I said earlier this morning, it is flawed.
4 It is seriously flawed data. We never get good data post-
5 marketing, and that's something that we have to grapple
6 with. We have to look at it piecemeal and we have to piece
7 the pieces together and get a whole from it somehow.
8 You're right. This committee made a
9 recommendation to the FDA four years ago and we're
10 revisiting that because there is now the perception, one,
11 that the playing field is no longer level and, two, that
12 there have been some things that have come to our attention
13 that have led to changes in the labeling. We feel that the
14 changes in the labeling are not consistent with an
15 unscheduled drug.
16 DR. STRAIN: Dr. McNicholas.
17 DR. McNICHOLAS: Yes. I have to agree with Dr.
18 Meyer, that I'm picking up a great deal of discomfort with
19 this whole process on a couple of levels.
20 One of the things that I think has been
21 remarkable is the sponsor made a huge effort to discuss why
22 they do not consider withdrawal per se to be an indicator
23 of abuse and dependence. I frankly would like to hear a
24 response from the FDA on why they do. Certainly the sense
25 within the medical community has been changing and evolving

1 over the past several years on where withdrawal
2 symptomatology and syndromes fit in the definition of abuse
3 and dependence. It has struck me throughout the day that
4 it seems to be a huge gulf between the two groups as to
5 where this falls.
6 Let me defer my other question until I get an
7 answer to that one.
8 DR. McCORMICK: I'm not sure I can speak for
9 everyone, although I'll try.
10 I don't think that we take issue with the
11 sponsor's assessment that withdrawal syndromes don't occur
12 in other settings. They clearly do. I think that what we
13 can say, though, is that the quality of the data that we
14 receive in post-marketing reports doesn't allow us to draw
15 that fine line. So, we're left with having to lump them
16 together.
17 DR. ALDERFER: I would agree with that. If we
18 want to try to make any kind of comparison, flawed though
19 they may be, with other drugs, we'll need to do some
20 lumping together.
21 Now, I don't think we're trying to say that
22 withdrawal syndrome is abuse. At least that's not the way
23 I was looking at it. But I think we got roughly half of
24 what's now -- we have about 553 reports in our system
25 currently as of today, and about half of those involve

1 abuse. So, that's not too far with what the sponsor is
2 coming up with. Our number of abuse cases is pretty close
3 to theirs.
4 DR. STRAIN: Dr. Andorn.
5 DR. ANDORN: Just a point of clarification. My
6 understanding is that scheduling is a legal definition more
7 than a definition than we can change today at this table.
8 And the eight factors have been predetermined. What we've
9 been asked to do is take a look at the data since marketing
10 and see if we, as the committee, would make a
11 recommendation to not schedule or to schedule on the basis
12 of our response to the eight factors. Am I correct?
13 DR. STRAIN: Dr. McCormick?
14 DR. McCORMICK: That is correct. We're not in
15 the position, we don't have the authority to change the
16 law. That is why we've framed the questions as we have
17 because we are looking to you for your assessment of the
18 matters that pertain to the science and we'll put them in
19 the context of the law.
20 DR. STRAIN: Dr. Young.
21 DR. YOUNG: I'm having trouble with the
22 comparator drugs. Dr. Meyer mentioned comparators of the
23 mu opiate type that under many conditions will act as full
24 agonists and some of the older agonists/antagonist
25 compounds.

1 But I would like to ask the FDA why you elected
2 not to include as your comparator drug some of the newer
3 compounds that have been released unscheduled. I'm
4 thinking of nalbuphine and the pre-nasal formulation of
5 butorphanol, both of which exert some of their analgesic
6 effects through a mu mechanism. I also understand that
7 dezocine is available by prescription unscheduled and
8 exerts its effects through those mechanisms. I wondered
9 what do those compounds look like in the various reporting
10 systems and why aren't they being used as part of the
11 comparators.
12 DR. KLEIN: Well, in the case of Stadol --
13 first of all, I'll talk about Stadol nasal spray.
14 DR. YOUNG: No. I said pre-Stadol nasal spray,
15 the pre-nasal Stadol. You've got Nubain and Stadol that
16 were available unscheduled by prescription as analgesics I
17 believe only by injection.
18 DR. KLEIN: It was only available by injection.
19 That limited its usefulness as a comparator because these
20 are drugs that are outside the retail level.
21 There has always been the argument also put
22 forward that these are agonists/antagonists or partial
23 agonists and that these are issues that tend to reduce the
24 drug's abuse liability.
25 What we were trying to do -- and of course,

1 we're looking for the best comparator as you are -- is to
2 recognize the impact of availability and distribution of
3 the drug, and that is an issue that impinges significantly
4 on its use as a comparator. To compare it to an injectable
5 product, a parenteral product that has limited distribution
6 that's not really going to be sitting around in someone's
7 medicine chest, it's not going to be left up to the patient
8 himself to administer brings in confounding issues that --
9 I really think that really eliminates that whole product
10 line as usefulness as a comparator.
11 Now, let me just tell you the way the Medwatch
12 works as far as my desk is concerned. I'll get a report
13 from Dr. Alderfer's group after a drug has been on the
14 market for a while, and they identify this conglomeration
15 of COSTART terms as a signal that the product is being
16 abused.
17 Now, this is what happened shortly after in the
18 case of Stadol nasal spray. You don't want me to talk
19 about that. Okay.
20 DR. STRAIN: Dr. Meyer.
21 DR. MEYER: I'd like to ask the sponsor a
22 question and really the same question to the FDA.
23 First, to the FDA, does dezocine and the pre-
24 nasal form of butorphanol carry the same warning label with
25 regard to potential for abuse?

1 And to the sponsor, how do they answer Dr.
2 McCormick's point with regard to the warning label that
3 went in in 1996 in an unscheduled drug, relative to what
4 would be in a schedule 4 or 5? I don't care who from the
5 sponsor answers.
6 DR. STRAIN: Perhaps we could hear from the FDA
7 first.
8 DR. KLEIN: There's a strong warning on
9 dezocine as far as a head-to-head comparison.
10 DR. MEYER: Now, does it say literally what the
11 warning label is, risk of abuse and dependence?
12 DR. KLEIN: I believe it does. I would have to
13 check.
14 DR. MEYER: So, you have unscheduled drugs that
15 give that same warning.
16 DR. KLEIN: Yes.
17 DR. STRAIN: Dr. McCormick, did you want to add
18 something to that?
19 DR. KLEIN: That's with some qualification
20 because I have to check the exact wording.
21 DR. McCORMICK: I just have to say this drug
22 predates my time, so I would have to look into this
23 further.
24 Stadol does but then it subsequently has been
25 scheduled.

1 DR. YOUNG: As the nasal spray.

2 DR. McCORMICK: No. All forms have been.

3 DR. CICERO: We're trying to get an answer to

4 this question.

5 The question has been coming up about the

6 comparator drug and the revisiting of 1994. I agree with

7 you completely, Roger. We are back to 1994. At the time

8 this was proposed, this was indeed an experiment, and it

9 was proposed to be an experiment because we didn't have any

10 comparator data. We spent an enormous amount of time at

11 that meeting and for three or four months afterwards with

12 the FDA trying to come up with comparator drugs. We

13 couldn't come up with any. There weren't any historically

14 that we could exactly trace and get the denominator and get

15 all the appropriate information that we needed. So, we

16 have been struggling. We are still grappling with it.

17 It gets back to Eric's point really, what is

18 low? If you look at amitriptyline, the rate of abuse of

19 Ultram is probably at that level. Or Prozac. Is that

20 meaningful? I don't know whether that's meaningful.

21 We don't have any comparative data. You can

22 make it look good or you can make it look bad. No one has

23 ever attempted before to do a study of this sort. So, we

24 seem to be spinning our wheels a little bit today, but

25 realizing that from day one four years ago, we knew

1 ultimately this day would come when we'd have to sit down
2 and say, okay, we've collected data in a systematic way.
3 Spontaneous reports are dropping off. We know that. That
4 gets to the issue that spontaneous reports reflect the
5 general population. The FDA tells us that. They've been
6 telling us that for 50 years that they reflect the
7 population. So, to say we're only screening drug-abuse
8 prone individuals I don't comprehend because we've got
9 spontaneous reports. Of course, we're surveying the
10 population at least as well as it has ever been surveyed
11 prior to this time.
12 DR. MEYER: But you didn't answer my question.
13 DR. STRAIN: Yes. You didn't answer Dr.
14 Meyer's question. An interesting response --
15 DR. CICERO: And the specific question was?
16 (Laughter.)
17 DR. MEYER: You have a warning label that you
18 put in in 1996 that was partly a response to your findings.
19 DR. CICERO: Right.
20 DR. MEYER: How do you justify having that
21 warning label in an unscheduled drug based upon Dr.
22 McCormick's comment?
23 DR. CICERO: Let me let the company respond to
24 that.
25 DR. BURTON: May I refresh my memory? The

1 question concerned the labeling changes that were --
2 DR. MEYER: Went in in 1996.
3 DR. BURTON: -- resulted in that new label
4 roughly about the time of the Dear Doctor letter. I wasn't
5 around. Collective memory I've just gathered, and Dr.
6 McCormick and I'm sure that our colleagues over there may
7 correct me if I'm wrong.
8 But essentially we submitted some labeling
9 changes to the FDA in the normal course of events when you
10 see data like this. We then had interchange and there was
11 to-ing and fro-ing. There were additional statements that
12 they thought were appropriate to add. They were added. We
13 ended up with the labeling we ended up with.
14 DR. MEYER: I understand. The question still
15 comes down to Dr. McCormick's point and that is, how do you
16 justify the labeling in an unscheduled drug?
17 And the question came down on the other side.
18 You have two drugs that are unscheduled. Do they have the
19 same warning label? And we don't have the answer to that
20 either.
21 DR. BURTON: Well, again, may I suggest that
22 it's a subjective review in that one comes to an agreement
23 with the reviewing division about labeling until you're
24 comfortable with that labeling for that product in whatever
25 prescription status it is at the time.

1 DR. MEYER: But the bottom line is if yours is
2 the only unlabeled compound with that warning label --
3 DR. STRAIN: Unscheduled.
4 DR. MEYER: -- unscheduled with that warning
5 label, how do you maintain that it doesn't need to be
6 scheduled? That's really the only question.
7 DR. BURTON: I don't know the answer to that.
8 DR. MEYER: Well, that's why I was trying to
9 ask it on both sides.
10 DR. CICERO: May I suggest we're getting into
11 very dangerous territory here because I'm hearing an
12 admission that the Controlled Substances Act actually will
13 limit exposure? Are we trying to reduce the population
14 exposure here? What is this "level the playing field"? I
15 don't understand what that means exactly.
16 DR. MEYER: That was not my term.
17 DR. CICERO: Well, the term was used "level the
18 playing field." I don't know what that means. If it's an
19 unfair competitive advantage, what does that mean?
20 DR. STRAIN: Let me interrupt. Dr. Meyer has
21 posed a question and while this is an interesting point, I
22 don't hear it responding to Dr. Meyer's question.
23 DR. CICERO: I don't think any of us have the
24 answer to the question.
25 DR. STRAIN: If that's the case -- Dr.

1 Jasinski, do you have the answer?

2 (Laughter.)

3 DR. JASINSKI: Just a comment. Roger, there is

4 no correlation between this. I just tell you this because

5 when you look at what happens in a label, they're

6 individual drugs, and just like the control decision and

7 the decision to write a label are political decisions in

8 the end, it's not entirely scientific. So, you can have

9 people putting things into warning labels just in a sense

10 to be broad, to cover themselves, to protect themselves.

11 You read the warning label. You take an antihistamine or

12 an antidepressant. You're not supposed to drive a car, for

13 example. So, when you look at this, the warning label is

14 essentially a legal document, a marketing statement, to

15 make the worst sort of case.

16 Whether it relates to the same decision in

17 terms of the Controlled Substances Act, meeting of the

18 criteria, it's a whole different issue. I don't think

19 they're related and I don't think it's inconsistent to have

20 something in the warning label and not controlled. I mean,

21 we don't put a warning label about the suicide potential of

22 acetaminophen or aspirin. Yet, if you look at the DAWN

23 data, if you look at a suicide drug, acetaminophen and

24 aspirin.

25 DR. MEYER: I'll just be quick. You're not

1 responding. The FDA isn't responding on the other side.
2 It's symptomatic of the problem, and the committee will not
3 be able to resolve it for both of you. You may have put
4 yourselves as the sponsor in an adverse situation in 1996
5 inadvertently.
6 I disagree with you completely that a warning
7 label is not relevant to scheduling with regard to abuse
8 and dependence. It is precisely on that issue that people
9 have argued about scheduling new benzodiazepines or new
10 GABA agonists. It becomes a critical issue.
11 DR. JASINSKI: The issue is relative risk. The
12 warning label just mentions it. It says nothing about the
13 relative risk.
14 DR. MEYER: But the issue is precedent and if
15 there is no other compound that is unscheduled that bears
16 that warning label, you worry the people on that side of
17 the table. If there are compounds that don't bear that --
18 DR. JASINSKI: Butorphanol was uncontrolled for
19 years, the injectable, and it said it was a narcotic.
20 DR. MEYER: And it said it had abuse potential.
21 DR. JASINSKI: Yes.
22 DR. MEYER: Then the point is that there is no
23 relationship and that there is no precedent, and the people
24 at the FDA shouldn't worry as much.
25 DR. JASINSKI: Right. The issue was raised of

1 nalbuphine. The issue was raised of butorphanol.
2 Propoxyphene was recognized as having a morphine-like
3 effect and for years was an uncontrolled substance. It was
4 controlled because it created a large number of deaths, and
5 it was found in medical examiner data which indicated a
6 large public health problem. So, yes, there have been
7 precedents where drugs have been uncontrolled with this
8 recognition of what we now call mu agonist effects.
9 In fact, we have this under our treaties and
10 under our laws. Technically we can have an exempt
11 preparation of codeine under the international treaty.
12 Technically we could still sell codeine cough syrups,
13 paregoric in drugstores over the counter. So, technically,
14 yes, even though it would have the same warning label.
15 DR. STRAIN: Thank you.
16 Dr. Simpson.
17 DR. SIMPSON: My point is fairly minor. But
18 Dr. Cicero kept saying that the number of reports were
19 dropping off, and as a statistician, I thought I'd just
20 have a look at it. If you group the quarters differently,
21 then in fact you could almost argue that they're going up,
22 not dropping off.
23 DR. STRAIN: Well, explain that to us. That
24 seems like a more than minor point.
25 (Laughter.)

1 DR. SIMPSON: Okay.
2 DR. STRAIN: So, perhaps you might elaborate on
3 that.
4 DR. SIMPSON: Whether it's statistically
5 significant or not is another thing, of course.
6 They're grouped --
7 DR. STRAIN: What volume are you in and what
8 page?
9 DR. SIMPSON: I'm on page 48.
10 DR. STRAIN: Page 48 of Dr. Cicero's December
11 report?
12 DR. SIMPSON: Yes, this one.
13 DR. CICERO: It's coming up on the screen.
14 DR. SIMPSON: I've got to make sure I've got it
15 the way I was doing it. I just wanted to show you that
16 it's not clear what's happening at the end. That's the
17 point I really wanted to make.
18 You see that slide unfortunately doesn't work
19 because it's by quarter, and I've got on my diagram the
20 number of reports by month, as well as number of reports by
21 quarter. My point is that the grouping of the reports by
22 month, if you do it differently -- I mean, after all, what
23 is a quarter? If you, for example, say, well, why not
24 instead of taking the quarter to finish at December, we
25 take it to finish in October? I think if you do that,

1 those of you who have it, will see that in fact the numbers
2 are beginning to go up again if you do it by quarter that
3 way. And it's less conclusive if you do it saying the
4 quarter ends in November. But again, there is a beginning
5 of a trend.
6 DR. STRAIN: Perhaps what you might do is read
7 out for us just the numbers by quarter since you've summed
8 them.
9 DR. SIMPSON: I haven't. I've done them in my
10 head.
11 DR. CICERO: We can get the numbers for you.
12 Recall that there is that one event with New
13 Orleans that occurred that disappeared as rapidly as it
14 occurred.
15 DR. SIMPSON: You know, the thing that we
16 statisticians always try to point out, that there are
17 random fluctuations and it's only too often. For example,
18 in my pediatric department if, for example, money is
19 starting to come in, she says, this is great, but then of
20 course if it goes down a bit, she's going to say, well,
21 nobody is working hard.
22 (Laughter.)
23 DR. SIMPSON: So, this is the point I'm making
24 is that it depends how you look at this. It's not
25 conclusive that the number of reports are going down. By

1 simply playing with the figures, I can make them go up is
2 what I'm saying.
3 DR. CICERO: I will give you the numbers for
4 1996 and 1997. I'd love to see how you do this. By month.
5 18, 15, 28, 17, 11, 28, 10, 15, 27, 5, 9, 9, 8, 4, 10, 4,
6 14, 5, 26, New Orleans again, 12, 7. I'd love to see how
7 you group those and had that going up.
8 DR. SIMPSON: Going up at the end. Well, if
9 you take October --
10 DR. CICERO: If you just look at the graph, how
11 could that go up?
12 DR. SIMPSON: It's beginning to go up is what
13 I'm saying.
14 DR. CICERO: We'll have dueling statisticians,
15 and I'll have my statistician from Johns Hopkins get up and
16 discuss this because you are raising an extremely important
17 point very late in the day, and I think we need to address
18 the fact that this is an artifact.
19 DR. SIMPSON: It's beginning to go up again if
20 you group it differently. If you take from October back,
21 it's 6, 26, and 5 is 37. Going back again, you've got 33.
22 Going back another three, you've got 22. Going back
23 another three, you've got 23. Now, it's beginning to go
24 back up to the lump again.
25 DR. CICERO: In the month of January, February,

1 and March of 1998, which we have not completed yet, the
2 numbers are 6, 8, and 9. That's not complete. It's not on
3 this graph. So, is it going up or is it going down?
4 DR. SIMPSON: 6, 8, and 9. I don't know.
5 DR. CICERO: It's not on the graph. It's the
6 first three months of this year.
7 DR. SIMPSON: I'm just checking. Yes, it is.
8 DR. STRAIN: I have people whispering to me to
9 stop this.
10 (Laughter.)
11 DR. STRAIN: I agree. This reminds me that
12 Disraeli said there are liars, damned liars, and
13 statistics.
14 (Laughter.)
15 DR. SIMPSON: I just wanted to bring up the
16 point that it's not clear where it's going. That's the
17 point I really wanted to make.
18 DR. STRAIN: Other questions? Dr. McNicholas.
19 DR. McNICHOLAS: Yes. I have a question based
20 on a question you asked earlier.
21 DR. STRAIN: Actually, before you start, after
22 your question, I'd like to start to hone us in to the three
23 questions.
24 DR. McNICHOLAS: This actually refers to the
25 last of the three questions. Your question earlier was

1 when somebody saw problems in 1996, there was a meeting.
2 Who initiated the meeting and would the FDA have initiated
3 the meeting if the sponsor did not? If the sponsor in fact
4 did, did the independent steering committee have a major
5 role in initiating the Dear Doctor letter and in calling
6 attention to the number of reports that were of
7 significance in early 1996?
8 DR. STRAIN: Dr. McCormick?
9 DR. McCORMICK: I'll have to call on the review
10 division because they would have initiated the meeting I
11 believe. Dr. Weintraub or Dr. Hyde?
12 DR. WEINTRAUB: That's a very important
13 question obviously.
14 DR. HYDE: I'd have to check the record as to
15 exactly who contacted who. Certainly the division had been
16 monitoring the issue, and no matter if the sponsor had not
17 met with us and there was other business going on, we would
18 have met with them. It was an issue that we monitoring
19 that and the seizure thing. We were looking at the
20 reports. We thought there was a qualitative difference
21 from what we might have expected based on what we had when
22 we made our original product approval, and we wanted to
23 discuss with them also to get some information on what, if
24 anything, had been learned from the steering committee at
25 that point. That was only after about nine months that the

1 product had been on the market.

2 DR. STRAIN: Dr. Cicero, did you have a

3 response to that question from the sponsor's side? The

4 same question.

5 DR. CICERO: I think again it was one of those

6 mutual issues. The steering committee had volunteered with

7 Dr. Wright in particular -- the communique was mainly in

8 that direction -- to come and present the data as often as

9 possible. We presented it in early 1996, about six weeks

10 before the letter came out, and then again about six to

11 eight months later and presented our data at that time.

12 That certainly was a contributing factor.

13 Who -- did the steering committee -- I can't

14 answer the question of who called the meeting, but was it

15 instrumental? Yes, it was.

16 DR. STRAIN: Dr. Weintraub, did you have a

17 comment?

18 DR. WEINTRAUB: No.

19 DR. STRAIN: Dr. Burton, did you have a

20 comment?

21 DR. BURTON: Without wishing to sound contrite,

22 I think we were the party to the second part. I have a

23 feeling that at that time, as the reviewing division were

24 beginning to start thinking about some of the reports they

25 were receiving, there was no doubt that the sponsor, i.e.,

1 Ortho-McNeil/PRI, was sending in proposed labeling changes.
2 The independent steering committee wouldn't have been
3 necessarily involved in some of those proposed labeling
4 changes, although I believe Ted would have known about it.
5 I have a feeling that it was six of one and a half dozen of
6 another and it just highlighted everything. And the
7 changes came about from actions from both sides.
8 I'm sure Dr. McCormick will correct me if I'm
9 wrong, but I get a distinct sense and feeling that that was
10 how it came about.
11 DR. STRAIN: It sounds very organic.
12 (Laughter.)
13 DR. STRAIN: Any other questions?
14 DR. de WIT: I have one relatively minor
15 question. It looks like the rates of abuse reports went
16 down after the letter and after the labeling change. Is
17 that right? Did the rate of prescription go down
18 correspondingly at that time?
19 DR. BURTON: From my memory of the prescription
20 chart, it faltered. It didn't fall. If it did fall, it
21 didn't fall significantly, so that it sort of leveled off
22 or dipped a little bit but then continued going up
23 afterwards. I think that that dip or stability was only
24 over a period of six to eight weeks.
25 May I just add that that is very typical of a

1 response from the marketplace both in the U.S. and
2 elsewhere in the world when a Dear Doctor letter is issued.
3 That's a very common observation.
4 DR. de WIT: So, to what do you attribute this
5 decline over about a year in the reports of abuse?
6 DR. BURTON: In reports of abuse, with any
7 spontaneous reporting scheme, when a product goes on the
8 market, there's usually a flurry of reports that come in
9 and that just dies away. Now, normally it's a period of
10 about four or five years before you get over the hump of
11 the maximum reporting rates, and that dies down. This
12 seems to have occurred earlier, but nevertheless I think
13 the perceived wisdom might be that it is related to a
14 combination of perhaps lower reporting rates but also
15 familiarity with the drug on behalf of the prescribers and
16 the users.
17 DR. CICERO: I think that would only apply to
18 spontaneous reports. The rate has been dropping despite
19 active solicitation of reports by the committee. So, the
20 only interpretation of that data is the actual number of
21 abuse cases is dropping which we would suggest reflects
22 experimentation which occurred in 1996. Our
23 questionnaires, our informants continue to respond with
24 cases and report to us. They're seeing less and less and
25 less. That's the only explanation for the overall rate

1 decline. There can be no other explanation. Spontaneous
2 reporting is dropping off because of time.
3 DR. STRAIN: I know I wanted to get to the
4 three questions. Dr. Cicero, if I could just ask you a
5 totally different topic that we have never touched on, the
6 chronic pain patient population study. Three groups, 3,000
7 patients per group?
8 DR. CICERO: 4,000 patients per group.
9 DR. STRAIN: Because it's not clear. At times
10 you contradict yourself I think in your report on that.
11 And there have been how many patients? There
12 have been 4,000 enrolled so far roughly?
13 DR. CICERO: 8,600.
14 DR. ADAMS: Slightly over 8,000.
15 DR. CICERO: Slightly over 8,000.
16 DR. STRAIN: And what's the primary outcome
17 measure in this study?
18 DR. CICERO: Go ahead. I'll let Edgar Adams
19 answer that question.
20 DR. ADAMS: Well, first, we have slightly more
21 than 8,000 patients enrolled. The NSAID/Ultram arm is
22 almost full. The Ultram arm is almost full, and the other
23 arm, the hydrocodone/Ultram arm is lagging. That's because
24 it's prescribed less.
25 The outcome measures are an abuse index that

1 has four basic components. They span about -- I don't know
2 -- 30 questions. There is also the complete SF-36
3 functional status assessment as an outcome measure, and
4 there's also a self-rating of benefit and pain scores, as
5 well as the audit. The audit is an explanatory variable,
6 as is the pain-related control scale. Helplessness
7 subscale is also an explanatory variable to look at the
8 vulnerable population. But the primary outcome measures
9 are the SF-36 functional status assessments and an abuse
10 index.
11 DR. STRAIN: Thank you.
12 Let us turn to the three questions. These
13 questions to be posed to the committee are not yes or no
14 questions by and large, which means that we could have yet
15 further discussion. I would suggest let me begin by
16 reading the first question, opening it up for discussion
17 and let us see if we have some consensus in the committee
18 regarding a response to the question. If anybody feels
19 that they have a brilliant response that will capture the
20 spirit of the afternoon, please speak first.
21 The first question is, consider the new
22 information about tramadol obtained since the last DAAC
23 meeting and since marketing. What are your opinions with
24 regard to the potential for abuse of this product?
25 Dr. Meyer, would you like to take a --

1 DR. MEYER: I spent some time before talking.
2 Let's hear from some of the other people.
3 DR. STRAIN: Okay.
4 (Pause.)
5 DR. MEYER: Eric, I think that the case has
6 been made with regard to certain subpopulations, that there
7 is a risk which was highlighted in the 1996 changes in the
8 labeling. I think that your point with regard to other
9 drugs in that population is also a valid point.
10 The other piece, which is the independent risk
11 of abuse with regard to just as the drug is prescribed for
12 acute pain, as in the examples that were presented by Dr.
13 Alderfer, I think bear additional scrutiny and inquiry. I
14 think an individual case report like that is not yet at
15 this time sufficient, but I think it's an issue that does
16 need to be further explored because I think that would move
17 this to a different level of concern.
18 DR. STRAIN: I see other people nodding their
19 head yes. Dr. McNicholas?
20 DR. McNICHOLAS: I was just going to say I'm
21 not sure that we're that much further along than we were in
22 1994, and part of that is that we really don't have
23 anything to compare it to. In 1994 nobody ever said that
24 this drug had no abuse potential. It was thought to be
25 low. Low compared to what? High compared to what? We

1 still don't have a good answer to those questions.
2 Certainly from the data that we have seen today
3 and that we were presented with, it doesn't look like it
4 took off like a rocket in the drug abuse population. It
5 was not a total sleeper. So, I don't know how we can
6 answer that question without a fair comparison, and this is
7 really the issue that came up in 1994. The committee kind
8 of felt that we had a new animal. You had an analgesic
9 with mixed activity with a probable some abuse potential,
10 but nobody knew how much. I'm not sure that we're not
11 still kind of at that same place. We don't have something
12 that we can appropriately compare this to and certainly we
13 have not been shown today something that we could
14 appropriately compare it to.
15 DR. STRAIN: Thank you.
16 Others? Dr. de Wit.
17 DR. de WIT: I agree we're handicapped by not
18 having a comparison drug, although I think it's difficult,
19 since we would be probably be comparing a non-scheduled
20 drug to a scheduled drug. So, that's going to be an almost
21 impossible comparison.
22 I'm reassured, looking at the two graphs -- the
23 graph prepared -- looking over time, at the reports of
24 abuse over time, the sponsor presented one across the two
25 and a half year period, and the FDA based on the

1 spontaneous reporting system. And there is a very good
2 correspondence in the pattern of reports; that is, there's
3 a peak at a very particular time over basically the second/
4 third quarter of 1996, and then that declines. It's nice
5 to see it in two reporting systems, and so it sounds to me
6 as though there really has been a decline in reports since
7 it's from two independent sources.
8 So, I wooled very cautiously say that it might
9 be worth seeing whether it remains low and depend not only
10 on the sponsor's reporting system, but also on the FDA's
11 reporting system to see whether this trend continues.
12 DR. STRAIN: Dr. Young.
13 DR. YOUNG: I would say that I don't see
14 anything in the pattern of data presented today, especially
15 given that this is a new drug, to argue that we need to
16 move away from the course taken in 1994.
17 But I also think that I was disturbed today to
18 hear that the independent steering committee is now on a
19 one-year renewable contract. At my institution, those are
20 not very stable ways of maintaining long-term surveillance
21 systems. So, I think that the notion of having the sponsor
22 take a proactive, aggressive role in terms of looking at
23 the way this compound -- the patterns of use for the
24 compound needs to be continued.
25 DR. MEYER: Let me elaborate on that because I

1 think that's an important point.

2 DR. STRAIN: Yes.

3 DR. MEYER: I think that it also is important

4 that the reporting relationship of the independent

5 committee also be to the FDA, as well as to the company.

6 DR. STRAIN: I believe it is. Dr. Cicero, do

7 you want to respond to that?

8 DR. CICERO: The company is committed for as

9 long a term as we wanted for this post-marketing

10 surveillance committee. Indeed, I must take the credit and

11 the committee takes the credit for the one-year renewable.

12 It was our insistence. We could have asked for two or

13 three or four. I think the problem was just to put it on

14 sort of a regular basis for renewal.

15 We as an independent steering committee are

16 committed to follow this through for the very points that

17 you're all raising. This was an experiment in 1994.

18 You're correct. It's ongoing. Trends in data are

19 occurring. We need to look at it for another year.

20 It's our judgment we don't have a severe public

21 health threat here. I think the circumstance hasn't

22 changed much since 1994. The rate is as low as we thought

23 it was. We're gathering data. The next 12 months should

24 address that.

25 I lost track of the other point I was trying to

1 get to.

2 DR. MEYER: Who do you report to at the FDA?

3 DR. CICERO: We tried to give reports directly

4 to the FDA and were informed by the FDA that we were un-

5 allowed to do that. They had no mechanism to handle

6 independent reports coming from us via Dr. Curtis Wright.

7 He said it needed to come through the regular submissions

8 from the sponsor. As you saw in the insert, I write a

9 letter to the sponsor saying please communicate this to the

10 FDA.

11 DR. MEYER: I'm uncomfortable with that because

12 the FDA really does have the public health responsibility

13 here.

14 DR. CICERO: In 1994 we were told that there

15 was no mechanism by which they can receive a report other

16 than through established channels because of the uniqueness

17 of the steering committee's composition.

18 DR. McCORMICK: Why can't you submit the report

19 to the NDA?

20 DR. CICERO: We do and then it's submitted to

21 you. But what I'm hearing suggested and we have suggested

22 for years is we should be giving a report to the FDA, and

23 we were told that's not possible.

24 DR. McCORMICK: That's what you do when you

25 submit it to the NDA.

1 DR. CICERO: But it's going through the
2 sponsor.
3 DR. ANDORN: Could they give the report to this
4 committee, to the DAAC?
5 DR. CICERO: And we would be delighted to give
6 the report to NIDA. We suggested that in the beginning to
7 NIDA and the FDA, but apparently there was no mechanism
8 available for us to do that.
9 DR. KLEIN: We get summary reports from the
10 sponsor on a monthly basis. We don't get the details of
11 the independent steering committee.
12 DR. STRAIN: Could I suggest that -- I think I
13 speak for the committee -- if there is a mechanism that the
14 FDA can work out for direct communication between the
15 independent steering committee and the FDA, that that would
16 be -- and I'm seeing multiple heads shaking yes.
17 DR. CICERO: Vastly preferable from the
18 independent steering committee's viewpoint as well. We
19 would prefer that. We were told it was not possible. If
20 something can be worked out, we would be delighted. It
21 further establishes our independence.
22 DR. McCORMICK: I would vote for that as well.
23 I would caution you, though, that the question
24 that we're attempting to answer, that we're trying to
25 elicit from you, is a very separate question from the

1 independent steering committee. Those really must be
2 answered on a separate track.
3 DR. STRAIN: Right. We have strayed from the
4 first question. Thank you.
5 DR. MEYER: Well, actually that's in number 3.
6 DR. STRAIN: Yes.
7 DR. MEYER: And that would be our
8 recommendation under number 3, including consideration of
9 comparator drugs that might be put into this same mix.
10 DR. STRAIN: Shall we jump to number 3 and
11 finish that?
12 DR. MEYER: We've done number 3.
13 DR. STRAIN: We have to give others a little
14 bit of a chance.
15 Question 3 let me just read. The agency would
16 like to obtain the committee's comments on the ISC as a
17 successful deterrent to the abuse of the drug or as a
18 useful post-marketing tool to evaluate evolving patterns of
19 abuse. Please also explore possibilities for the future
20 mission, goals, and duration of the ISC.
21 Dr. Frank.
22 DR. FRANK: I would want the steering committee
23 to do a more comprehensive study of drug users. Recent
24 work that I've been doing really has heightened my
25 awareness of a large street drug-using population, an older

1 population, a liver-impaired population, a population in
2 pain that's looking for analgesia. A good part of that
3 population is not in the health care system for a variety
4 of reasons. So, they are not under the watchful eye of
5 doctors, physicians, or educated sales people, but get
6 their drugs from irresponsible pharmacists, and street drug
7 users, sell them back and forth, use more than they should,
8 and are getting into trouble with these drugs. This is as
9 a result of street studies we've done and focus groups with
10 these drug users. Now, there is no way of monitoring these
11 people, but they complain that they're getting in trouble
12 with other drugs.
13 So, I throw that out to you here. In New York
14 City, I speak for about a quarter of a million street drug
15 users.
16 DR. STRAIN: Thank you, Dr. Frank.
17 Other comments? Dr. Khuri.
18 DR. KHURI: I certainly agree with Dr. Frank
19 that's the problem with the so-called high school studies
20 and many of the other polls of drugs and who is using
21 drugs, it's hard to catch those people.
22 But I would like to speak for the ISC as a
23 really rather brave experiment I think. Dr. Meyer called
24 it a leap into the unknown. I find it an extremely
25 valuable source of information which broadens. It casts a

1 wider net than we have had before for post-marketing
2 surveillance.
3 I don't like the acronym PMS. It still gives
4 me a headache.
5 (Laughter.)
6 DR. KHURI: I do kind of like ISC, but we could
7 think of another acronym.
8 But I think its use could be broadened. I
9 don't want to get global here. I think it has been very
10 useful in this case. I would like to see it perpetuated
11 for as long as possible and ostensibly applied even to
12 other drugs. I think it has had a very good effect in this
13 case.
14 DR. STRAIN: Dr. Andorn.
15 DR. ANDORN: I have a couple comments. I think
16 that communication needs to be direct, but it needs to be
17 directed both directions, not just from the steering
18 committee to the FDA but also hopefully directly from the
19 FDA to the steering committee.
20 The second comment I have is it's clear this
21 costs a lot of money. Can every pharmaceutical company
22 that brings a product forward mount this kind of
23 independent steering committee, and if not, is this a
24 precedent that should be set, or could it be set in some
25 different way by, say, the same mechanism that's done with

1 the new drug applications where there's a contribution for
2 an independent council that would be jointly sponsored,
3 supported out of a pool of funds rather than just dependent
4 on the company that's bringing the proposal forward?
5 DR. STRAIN: Dr. de Wit.
6 DR. de WIT: I have another comment about the
7 mechanism. I know we're calling it the independent
8 steering committee, and I think we all recognize that it
9 isn't completely independent. I think one of the
10 liabilities here is that if we leave it completely in the
11 hands of the sponsor, we may see some redefinition of
12 what's meant by drug abuse or drug dependence to suit the
13 purpose. I think that we need to build something in, some
14 kind of mechanism into these overview committees to make
15 them truly independent or to make them interact with the
16 FDA or with our committee to make sure that there's some
17 agreement on what gets defined because clearly they're
18 defining substance abuse in a different way from what we
19 traditionally define substance abuse and dependence. We
20 need to protect ourselves if this is going to be a
21 mechanism that we use on a repeated basis.
22 DR. STRAIN: Yes. I actually had a similar
23 thought that if I could rewind the tape back to 1994, an
24 alternate mechanism might have been to have the sponsor, if
25 possible, transfer funds to NIDA and make it a competitive

1 grant application for studying this for five years, which
2 would have I think been an alternate novel mechanism that
3 might have been effective. But we can't rewind the tape
4 unfortunately.
5 Other comments for the third question?
6 I guess I would just also echo perhaps
7 conceptually as the two studies, post-marketing survey
8 studies, wind down, it may be appropriate to consider
9 whether there are other studies the ISC might consider such
10 as broad-based urine testing in particular populations,
11 something which there was a lot of discussion about back in
12 1994. So, that may be another study.
13 Dr. McNicholas.
14 DR. McNICHOLAS: Yes, just a couple of things.
15 First of all, there's the question here of whether the
16 committee is a successful deterrent to the abuse of a drug.
17 Frankly, I don't think it was ever set up to be a deterrent
18 to the abuse of the drug. It was, to my recollection, set
19 up to be a monitoring mechanism to try and raise flags
20 early, not later. So, I don't know that we have an answer
21 to whether or not it's a successful deterrent to drug
22 abuse. I'm not quite sure what successful deterrents to
23 drug abuse we have.
24 DR. KLEIN: Excuse me.
25 DR. STRAIN: Yes, Dr. Klein.

1 DR. KLEIN: There is the issue of intervention
2 where the ISC is supposed to intervene when they receive
3 reports.
4 DR. McNICHOLAS: Okay. From what we've heard,
5 they apparently did attempt to work with the company to
6 reeducate their sales market, et cetera. Actually I was
7 glad to see that the company then surveyed the physicians
8 to see whether or not the physicians were receiving the
9 message that they were supposed to be receiving, and I
10 would like to see more data on that, the truth be known.
11 The other thing that I would like to see more
12 data on is more of a general survey because while I think
13 that the idea that drug abuse populations is where you're
14 going to see a problem is probably appropriate, I also have
15 to agree with the FDA's position that it's not necessarily
16 the only population where you're going to see a problem.
17 Perhaps either working with some of the large sampling
18 surveys or doing one on their own to see whether or not
19 there is a general problem in Missoula or wherever rather
20 than just in the major urban areas in the northeast.
21 DR. STRAIN: Dr. Meyer.
22 DR. MEYER: I just have to run. If you get
23 through to number 2, I thought basically those points I
24 made in connection with that -- the issue of precedent I
25 think has been adequately discussed and the fact about

1 international scheduling also is an important precedent.
2 I think again the most important thing would be
3 to really try to make this committee clearly accountable to
4 the FDA in a direct way and to have the kinds of input that
5 people have been suggesting.
6 This issue shouldn't go away. The question of
7 scheduling ought to remain on the table as an issue, but I
8 think we need to see what happens with the rest of the
9 data.
10 DR. STRAIN: Dr. Klein?
11 DR. KLEIN: I know you have to run, but we
12 really weren't going to include a discussion of the
13 international review of drugs for international control.
14 Not only does that take into account different data sets,
15 but it takes into account different criteria that have to
16 be weighed as well.
17 DR. MEYER: I think the issue of the precedent
18 is a tricky one. I think you have to assert public health
19 control and accountability, and I think there are ways to
20 do that through the mechanism that was set up in 1994 until
21 we have further data.
22 I have to run.
23 DR. STRAIN: We have one more question. Did
24 you have a comment, Dr. Khuri, before that?
25 DR. KHURI: Yes, just very briefly. The ISC as

1 a monitor has a major difference. I think it was Curtis
2 Wright who said in one of the transcripts, they can't send
3 you to jail, which is a crucial difference. But I'd rather
4 be monitored by esteemed and compassionate and
5 sophisticated colleagues and am more apt to be open and
6 honest with them than a managed care company. There are
7 many managed care companies now monitoring our
8 prescriptions, and I could talk quite a bit on that but I
9 won't.
10 (Laughter.)
11 DR. STRAIN: Thank you.
12 Dr. Young.
13 DR. YOUNG: I think one other thing I would
14 like to see the ISC consider looking at is the relationship
15 between what makes a compound an effective analgesic in
16 severe pain patients and what limits the potential abuse of
17 the compound because it seems to me that the various
18 unscheduled opiates at this point, nalbuphine in
19 particular, is a less effective analgesic than this
20 compound appears to be. Is there something in the profile
21 of this compound or are there other things that the ISC is
22 learning that can provide guidance as to how what makes a
23 compound a clinically useful analgesic in the case of
24 strong pain and yet protects the public health with respect
25 to abuse liability? I didn't see much in the discussion

1 presented here that considered those types of comparisons,
2 and you're in a unique place to do it.
3 DR. STRAIN: Let us move then to the second
4 question, which is now the last question. Are the reports
5 of clinical abuse (actual) and pharmacological features of
6 tramadol similar to other opioids which are scheduled in
7 the CSA? If so, which ones?
8 Dr. Andorn.
9 DR. ANDORN: I'll take a bit of a leap here. I
10 think pharmacologically certainly preclinically it does
11 behave as an opiate. I think the delay in onset, due to
12 the fact that it's the major metabolite that behaves like
13 the opiate, is probably what results in the relatively low
14 numbers if you take the DAWN data and the actual numbers
15 of, say, 19 cases supposedly for last year of dependence
16 and 59 cases of recreational use of this compound versus
17 2,000 for codeine, 2,000 and 1,000, respectively, and maybe
18 the reason is the delay of onset because it is the first
19 metabolite. However, if the question is preclinically does
20 it behave as an opiate, the answer is yes.
21 So, qualitatively I'm very concerned that this
22 is a compound that could lead to abuse and certainly
23 physical dependence is known. Quantitatively I'm not so
24 sure because I don't think we've seen all the numbers.
25 One of the things I would throw out to whoever

1 goes on to study this is a lot of practitioners do
2 prescribe compounds in combination to potentiate analgesia,
3 and instead of looking for one compound as the comparator,
4 maybe looking for amitriptyline/acetaminophen combinations
5 that are prescribed might turn out to be a good comparator
6 for this particular compound.
7 DR. STRAIN: Thank you, Dr. Andorn.
8 Other responses to that question? Dr. de Wit?
9 DR. de WIT: I don't feel that we have adequate
10 data to make comparisons to other drugs that are scheduled
11 in the CSA.
12 DR. STRAIN: I see others nodding yes on that.
13 DR. KHURI: I agree with both Dr. de Wit and
14 Dr. Andorn's comments.
15 DR. STRAIN: Dolores --
16 DR. KLEIN: Excuse me.
17 DR. STRAIN: Yes.
18 DR. KLEIN: Dr. de Wit, could you just expand
19 on that because I heard Dr. Andorn reflected the
20 preclinical data and now we have a meeting of minds.
21 DR. de WIT: Yes. I'm referring not to the
22 preclinical, but rather to the reports of actual abuse over
23 the last four years. I don't think that we have enough
24 quantitative comparative data comparing other drugs that
25 are currently scheduled or other drugs that are not

1 currently scheduled to make the quantitative comparisons,
2 especially over the four-year period. I think that would
3 have been very useful to look at.
4 DR. McCORMICK: May I just ask, what would you
5 like to see? We've gone over this numerous times today.
6 We've seen this piecemeal. This is what we normally do
7 get. We have an opportunity in the independent steering
8 committee to get some real data and it's four years later
9 and we're scratching our heads and saying we don't have
10 real data. What should we be asking for?
11 DR. de WIT: Well, as a starting point, I would
12 suggest selecting maybe three or four other drugs that are
13 in the same class or used for the same indication and
14 collecting just the same information on a monthly basis
15 like this of reports of abuse and similarly when you
16 present the data for the emergency room visits or the
17 spontaneous reports. You don't need to have just one
18 comparator drug because there might be errors in the
19 judgment or in the numbers, but just to get an idea of
20 where it fits compared to other drugs.
21 DR. McCORMICK: Now, again, we've seen those
22 comparative data in the Medwatch system. We've seen the
23 other drugs and the same flaws I think would exist in a
24 different database no matter how it's obtained with the age
25 of the drugs, the different pharmacokinetic profiles and so

1 on. So, all of those things aren't going to go away.
2 DR. de WIT: Right.
3 DR. STRAIN: Well, there are a couple other
4 things in the pipeline. There are the two studies that are
5 being conducted which will provide a different mechanism
6 for looking at what's going on with the compound, that
7 is --
8 DR. McCORMICK: And again we have comparator
9 drugs in --
10 DR. STRAIN: -- the chronic pain patients.
11 I don't know if it's possible, but is there a
12 way to look at -- one of the difficulties it seems is that
13 we're talking about tramadol in the first three years of
14 its existence. Can we look at another compound in the
15 first three years of its existence?
16 DR. McCORMICK: We have done that, as you saw,
17 with Daypro. That was a newly approved nonsteroidal anti-
18 inflammatory drug with a completely different profile.
19 DR. STRAIN: Beyond Daypro, though, could we
20 look at --
21 DR. McCORMICK: There hasn't been any.
22 DR. STRAIN: Yes, that's the problem.
23 DR. YOUNG: Well, that's the problem with the
24 database. As pointed out by the FDA and several speakers,
25 the databases aren't -- it's wishful thinking to go back.

1 It may be that what would be -- I agree with Dr. de Wit
2 about the types of information that were available if
3 you're talking about additional monitoring, but it also may
4 be that the independent steering committee needs to be
5 asking about those reference drugs as well, not going out
6 and monitoring and following up on them, but if there's a
7 group of drugs that are being sampled by the FDA in order
8 to provide a framework of comparators, then perhaps -- one
9 big problem is that there's one set of types of data you
10 get in the Medwatch or the DAWN systems, and there's
11 another type of data set that are being generated by the
12 independent steering committee. Should that independent
13 steering committee also be sampling questions about the
14 same four drugs?
15 DR. CICERO: Eric, if I could answer that
16 question. We had this problem from day one, and the
17 difficulty we have as the independent steering committee is
18 asking another company to provide us the type of
19 information that ONP has been willing to provide us. We're
20 not in a position to do that.
21 The FDA could, I think, help in this respect if
22 they're truly acting in this capacity, to help us get the
23 type of information. We need to get denominator
24 information. We need to get the same sources of
25 information that ONP has given us. The problem is there is

1 no database we can go into to find a drug, say, going back
2 to 1987 and following its pattern of sales, all the types
3 of things we'd get. We can't go back and get that unless
4 some other company was willing to share all their data with
5 us, and I can assure you they haven't been willing to.
6 DR. YOUNG: Or in a proactive sense, Dr.
7 Andorn's suggestion about a pool somehow of funds that were
8 used to do that sort of thing proactively to look at the
9 post-marketing patterns with compounds in this type of
10 class.
11 DR. STRAIN: Dr. Klein.
12 DR. KLEIN: Well, we would like to know if the
13 comparator data is available from Dr. Schnoll's study.
14 Now, here we have urine screens that have been carried out
15 on this population. This is comparator data that should be
16 submitted with the tramadol data.
17 DR. CICERO: There's a great deal of comparator
18 data available in Dr. Schnoll's study.
19 DR. YOUNG: So, I would echo that request.
20 Those types of data would be very useful in that context.
21 DR. KLEIN: Now, specifically in response to
22 your concerns about comparator data, the best comparator is
23 Stadol nasal spray, but that's not what you want to hear.
24 DR. YOUNG: But you could convince me I think.
25 DR. STRAIN: Dr. Simpson.

1 DR. SIMPSON: I'm running out of time like lots
2 of us.
3 But I was wondering whether or not maybe a
4 subcommittee could be formed to think about this problem.
5 As a statistician, when I hear, well, what sort of database
6 do we need and so on, I start thinking why are we focusing
7 on databases. Why not some sort of planned study? And I
8 just want to put that in. But I was wondering whether we
9 could maybe discuss this and we don't have to give an
10 answer right away on this.
11 DR. STRAIN: It's something to consider.
12 Ms. Yaroma, I just wanted to see if you have
13 any comments as the consumer rep. We've had several
14 chatterboxes, myself being guilty.
15 MS. YAROMA: I don't know. I just think with
16 this drug, right now it's expensive and I don't think we're
17 going to see that much more addiction until it gets
18 cheaper. I think it's going to be used on the street a lot
19 when it gets cheaper. That's usually the pattern.
20 I'd also like to see with the addiction if
21 people that are on tramadol and they have some period of
22 clean time, if they go back to their first choice, say,
23 cocaine. That's not been brought up but I've seen that
24 happen.
25 DR. STRAIN: Thanks.

1 One other quick bit of business. I believe
2 this is the last meeting for Dr. Khuri and Dr. Young. Is
3 that correct? As full members, yes. We'll get you back.
4 (Laughter.)
5 DR. STRAIN: So, our thanks to you for all your
6 efforts today as well as over the many other meetings.
7 If other is no other business, I'll entertain a
8 motion for adjournment.
9 DR. ANDORN: So moved.
10 DR. STRAIN: And so be it. Thank you all.
11 (Whereupon, at 5:03 p.m., the committee was
12 adjourned.)
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