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

ARTHRITIS ADVISORY COMMITTEE

SAFETY UPDATES:

ENBREL (ETANERCEPT), IMMUNEX
REMICADE (INFLIXIMAB), CENTOCOR

OPEN SESSION

Friday, August 17, 2001

10:05 a.m.

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P R O C E E D I N G S

Call to Order and Introductions

1
2
3 DR. WILLIAMS: I am James Williams. I am
4 the acting chair for this open session of the
5 Arthritis Advisory Committee, and welcome you all
6 here. We would like to begin by introducing the
7 members of the panel, and we will start with Dr.
8 Katona.

9 DR. KATONA: I am Ildy Katona, pediatric
10 rheumatologist from the Uniformed Services
11 University.

12 DR. ABRAMSON: Steve Abramson,
13 rheumatologist, NYU and the Hospital for Joint
14 Diseases.

15 DR. VOSE: Julie Vose, University of
16 Nebraska Medical Center, hematology, oncology, and
17 a specialist in lymphoma and transplantation.

18 DR. IADEMARCO: I am Michael Iademarco,
19 the Associate Director for Science at the Division
20 of TB Elimination in the Centers for Disease
21 Control and Prevention.

22 MS. MALONE: I am Leona Malone, the RA
23 patient representative.

24 DR. KEANE: My name is Joseph Keane,
25 Boston University. I a pulmonologist and a basic

1 researcher in the host immune response to
2 tuberculosis.

3 DR. CALLAHAN: Leigh Callahan, health
4 outcomes researcher and epidemiologist at the
5 University of North Carolina in Chapel Hill.

6 DR. WILLIAMS: Jim Williams,
7 rheumatologist, the University of Utah.

8 MS. REEDY: Kathleen Reedy, Advisors and
9 Consultants Staff, FDA.

10 DR. WOFSY: David Wofsy, rheumatologist,
11 University of California, San Francisco.

12 DR. ANDERSON: Jennifer Anderson,
13 statistician from Boston University.

14 DR. ELASHOFF: Janet Elashoff,
15 biostatistician, Cedars-Sinai and UCLA.

16 DR. LEE: Jong Lee, medical officer,
17 Division of Epidemiology, Office of Epidemiology
18 and Biostatistics, CBER.

19 DR. JEFFREY SIEGEL: I am Jeffrey Siegel.
20 I am a clinical reviewer in the Division of
21 Clinical Trials in the Center for Biologics at FDA.

22 DR. SCHWIETERMAN: Bill Schwieterman,
23 Branch Chief, Immunology, Infectious Disease,
24 Division of Clinical Trials, Center for Biologics.

25 DR. WILLIAMS: Thank you. We will ask Ms.

1 Reedy to read the meeting statement.

2 **Conflict of Interest Statement**

3 MS. REEDY: Conflict of interest statement
4 for the Arthritis Advisory Committee, August 17,
5 2001: The following announcement addresses conflict
6 of interest with regard to this meeting, and is
7 made a part of the record to preclude even the
8 appearance of such at this meeting.

9 Based on the submitted agenda for the
10 meeting and all financial interests reported by the
11 committee participants, it has been determined that
12 all interests in firms regulated by the Center for
13 Drug Evaluation and Research and the Center for
14 Biologics Evaluation and Research present no
15 potential for an appearance of a conflict of
16 interest at this meeting, with the following
17 exceptions:

18 In accordance with 18 United States Code
19 208(b), a full waiver has been granted to Dr. Julie
20 Vose. In addition, limited waivers have been
21 granted to Dr. Steven Abramson and Dr. Janet
22 Elashoff, which allows them to participate in the
23 discussions without voting privileges. Copies of
24 these waiver statements may be obtained by
25 submitting a written request to the agency's

1 Freedom of Information Office, Room 12A-30 Parklawn
2 Building.

3 In addition, we would like to disclose for
4 the record that Dr. H. James Williams has
5 interests, which do not constitute financial
6 interests within the meaning of 18 United States
7 Code 208(a), but which could create the appearance
8 of a conflict. The agency has determined, not
9 withstanding these interests, that the interest of
10 the government in their participation outweighs the
11 concern that the integrity of the agency's programs
12 and operations may be questioned.

13 In the event that the discussions involve
14 any other products or firms not already on the
15 agenda for which an FDA participant has a financial
16 interest, the participants are aware of the need to
17 exclude themselves from such involvement and their
18 exclusion will be noted for the record.

19 With respect to all other participants, we
20 ask in the interest of fairness that they address
21 any current or previous financial involvement with
22 any firm whose products they may wish to comment
23 upon.

24 DR. WILLIAMS: Thank you. We met this
25 morning to discuss some safety updates on the

1 currently approved TNF inhibitors. This is for
2 safety only and is not meant to be a comparative
3 discussion between the agents. We will begin with
4 the FDA presentation with Dr. Schwieterman.

5 **FDA Presentation**

6 **Objectives**

7 DR. SCHWIETERMAN: Thank you very much,
8 Dr. Williams, and welcome, members of the committee
9 and members of the audience and both sponsors.

10 [Slide]

11 I am going to begin with simply a couple
12 of slides presenting an overview of the objectives
13 of this particular meeting since we have done some
14 of these in the past before as an agency, but
15 probably in the interest of updating people it
16 would be helpful to put these into a general
17 context.

18 [Slide]

19 The FDA, and particularly the Center for
20 Biologics, periodically updates the Arthritis
21 Advisory Committee on products in development and
22 on any post-marketing data that have come to the
23 agency since the last meeting. So, this is a
24 periodic update that happens to involve
25 post-marketing adverse event data and, therefore,

1 is in the open public session. Many of the
2 earlier updates we give to the committee are
3 actually in closed session because they involve
4 proprietary information.

5 As in all such updates, we don't prepare
6 formal questions and there will be no formal
7 questions presented today. It is information only
8 to the committee for their information and, as I
9 point out in the next slide, for discussion. It is
10 a very important update I think because it is
11 important that we all be aware of the existing data
12 on post-marketing adverse events, and that the
13 committee be able to comment on these adverse
14 events, but it is equally important to mention that
15 there are limitations to data analysis in
16 post-marketing events and their interpretation.
17 Dr. Braun, immediately following my presentation,
18 is going to go into more detailed discussion about
19 the uses and limitations of these particular data.

20 As I mention on the bottom, which is
21 perhaps obvious to everyone but I think needs to be
22 mentioned here formally, it is very important I
23 think to keep the committee informed and we hope,
24 as a Center, to continue to update the committee on
25 all things in development so that the public and

1 sponsors and patients are best served.

2 [Slide]

3 There are four objectives of the safety
4 update. They are very general objectives because I
5 think it is going to be a very interesting
6 discussion and I think we are going to perhaps come
7 away from this meeting with other kinds of plans
8 and initiatives and ideas about how to proceed.

9 But just stated simply, we want to present
10 the reports of adverse events that have come to us
11 for the current anti-TNF modulating agents
12 currently on the market, Centocor's Remicade and
13 Immunex's Enbrel. Specifically, we want to orient
14 that around presenting changes to the package
15 inserts.

16 This is not a complete summary of all of
17 the adverse events that have been tabulated to
18 date. It is a large summary, admittedly, and
19 perhaps it will need to be discussed further in
20 other kinds of settings but it is geared around, in
21 large part, the changes that have resulted to the
22 package insert following the initial approval of
23 these agents several years ago.

24 We are also going to review ongoing safety
25 studies and finally, but perhaps most importantly,

1 provide a forum for discussion for our esteemed
2 experts here and expert rheumatologists on the
3 committee who can perhaps put this in perspective.
4 I am very glad that the sponsors, both Immunex and
5 Centocor, have come to provide their perspectives
6 because I think it is very important that we have
7 an open communication between sponsors, the agency
8 and this particular committee.

9 So, without further ado, I am going to
10 turn it over to Dr. Braun who is going to be
11 discussing the MedWatch adverse event data
12 reporting system.

13 **MedWatch Adverse Event Reporting System:**

14 **Value and Limitations**

15 DR. BRAUN: Good morning.

16 [Slide]

17 My name is Miles Braun. I am going to
18 talk to you about some of the limitations of
19 MedWatch adverse event data, also known as passive
20 surveillance data.

21 [Slide]

22 To do this and to give you an idea about
23 it, I will start with a specific example. There is
24 a patient who develops a fever of 39 degrees,
25 productive cough and malaise during TNF blocker

1 therapy, and the patient visits the physician and
2 the physician diagnoses pneumonia, and the patient
3 is started as an outpatient on a treatment of oral
4 antibiotics.

5 Now, the physician may say to him or
6 herself the TNF blocker may have played a role
7 here, or maybe that won't even happen. Certainly,
8 if the physician doesn't have the thought that the
9 TNF blocker might have caused this infection there
10 will be no adverse event report from the physician.

11 [Slide]

12 However, if the physician does consider
13 that possibility the physician might report the
14 event directly to the FDA, using the form that you
15 can find in the Physician's Desk Reference or
16 finding it on the Internet. In addition, the
17 physician may call one of the manufacturers,
18 depending on the manufacturer, and report that
19 event to the manufacturer who, in turn, is
20 obligated to report that to the FDA.

21 Now, both FDA and the manufacturer can
22 receive the reports from the physician. So, it is
23 possible that you could have the physician
24 reporting to both. Frequently neither the FDA nor
25 the manufacturer receives a report of an adverse

1 event.

2 [Slide]

3 This is the MedWatch form. This is the
4 mandatory form so this is the form that the
5 manufacturers submit to the FDA. Basically, it
6 really boils down to a one-page form. It is quite
7 simple. You can have attachments to it but
8 essentially you are talking about -- and I know you
9 can't read the little fine print there, but
10 basically the key fields here are a box where the
11 text of the adverse event is written in. So, the
12 physician can write it in or the company will type
13 in what the physician says, or whoever is making
14 the report says, and that is put in there. So, it
15 is not a standardized field. We call it in the
16 jargon an open text kind of field.

17 You have also a similar type field for
18 history and laboratory results, and then some
19 demographic information, drug dosage, name of the
20 drug. So, it is pretty straightforward. It is
21 pretty simple, and it is also pretty brief.

22 [Slide]

23 We use the term adverse event to
24 differentiate from the term reaction. When we say
25 reaction we mean that the adverse event or the

1 problem was caused by the product. We use adverse
2 event to say that it is really a suspected drug
3 reaction. We are not sure. We are uncertain about
4 the causality. Usually the adverse event follows
5 the product when we have an adverse event report,
6 but actually on further investigation we sometimes
7 find that the adverse event actually preceded the
8 administration of the product, but usually we do
9 have temporal association.

10 [Slide]

11 These reports do have value. The MedWatch
12 System is national. It covers the whole United
13 States and, in fact, there are also international
14 reports that are accepted. To a large extent,
15 these are from the manufacturers, these
16 international reports. It is a national system.
17 It generates signals. What we mean by signals in
18 our jargon of pharmacovigilance is a concern, a new
19 concern about a particular adverse event associated
20 with a product. It doesn't mean that there is a
21 causal association. It just means, "gee, maybe
22 this product is associated with this adverse event;
23 we hadn't thought of that before." New drug
24 reactions have been discovered using this type of
25 system.

1 The system is also suited to monitor
2 previously identified safety concerns. So, say, in
3 a clinical trial you saw one really bad case of
4 something, X disease, in 300 patients or 500
5 patients, well, in the post-licensure period there
6 are thousands, hundreds of thousands of patients
7 treated and there is an opportunity to further look
8 at that.

9 Multiple drugs are given with products
10 after clinical trials. Just about any product on
11 the market can be given with the one of interest.
12 So, there are multiple opportunities to find new
13 drug interactions.

14 High risk individuals can be identified
15 too because in clinical trials usually the patient
16 populations are restricted and when you get out
17 into the post-licensure period just about anybody
18 can receive a product as well. So, this is what we
19 call real-world use. Whatever the real world does,
20 this is what we are looking at with these kind of
21 reports.

22 [Slide]

23 There are important limitations of these
24 data, and many of you are aware of these. As we
25 saw in the example, there is under-reporting. Many

1 reports of adverse events, even causally associated
2 adverse events, are not reported to the FDA or the
3 manufacturer.

4 Another limitation I alluded to, and it is
5 important to underline it, is just because there is
6 an adverse event report it does not mean that the
7 product caused the adverse event.

8 The nature of these forms is such that
9 individuals filling them out leave out data, just
10 like all of us do sometimes when we fill out forms.
11 Similarly, I think when the company personnel are
12 filling out the forms for a variety of reasons
13 these fields may not be completed. Sometimes the
14 information provided is incorrect. On rare
15 occasions it is coded wrong or the data is entered
16 wrong, and diagnoses can be wrong as well.

17 Duplicate reports -- for example, a
18 patient has an adverse event -- the patient I gave
19 in the first example, and the physician reported
20 that adverse event to the FDA but also the
21 patient's pharmacist reported it too. So, then we
22 have a problem where we have two reports about the
23 same event and in practice it can be difficult to
24 actually identify those duplicate reports and, to
25 use our jargon, de-duplicate it or remove one of

1 the duplicates or merge them.

2 The form, as I showed you, has open text
3 fields so the collection of the data is somewhat
4 non-standardized. In addition, diagnoses are not
5 standardized. What one physician calls anaphylaxis
6 another physician might call urticaria and dyspnea.
7 So, that is an issue when we review these reports.

8 Concomitant drugs -- again, this is an
9 ongoing issue in pharmacovigilance, and I think
10 today you will see that it is going to come up a
11 number of times. These products are frequently
12 given with corticosteroids or methotrexate and
13 these are important issues to take into account in
14 trying to interpret the data.

15 Long latency conditions -- the MedWatch
16 System, passive surveillance, is best suited to
17 pick up adverse events that occur in close temporal
18 association with the product. So, adverse events
19 that occur a year later, two years later are not
20 very well suited to be detected by this kind of
21 system.

22 [Slide]

23 Despite these limitations, it is important
24 to note that clinical trials, despite their very
25 tight and rigorous scientific designs, have

1 limitations. The numbers of patients usually don't
2 provide the statistical power to detect rare
3 adverse events. The characteristics of the
4 patients are limited. As I mentioned, a classic
5 example is pregnancy. Usually that is an exclusion
6 from many clinical trials and that will occur
7 inadvertently in use post-licensure.

8 Off-label use -- when products are
9 licensed they are given at different doses than
10 recommended. They are given in different diseases
11 than that for which they were licensed. So, that
12 is also an issue. The duration of use and
13 follow-up is generally less than you can have after
14 licensure. Usually there is an unlimited period of
15 follow-up after licensure and, certainly, with the
16 products we are talking about today there is a
17 relatively longer period of use than could have
18 been studied prior to licensure.

19 Geographic coverage is restricted
20 sometimes in pre-licensure trials but not
21 afterwards. Again, this issue of concomitant
22 medications is going to keep coming up. An
23 interest of the Food and Drug Administration and
24 the Public Health Service currently is medication
25 errors. One type of medication error is mixing up

1 two products because the names sound similar or
2 because the packaging is similar. That is unlikely
3 to occur in a clinical trial but afterwards there
4 is more opportunity for that.

5 [Slide]

6 So, when we try to put these data in
7 perspective, as I think we will be struggling to do
8 today, incidence rates are something that we want
9 to know. We want to know how many adverse events
10 occur for a certain number of patients treated but
11 we don't know that, because of under-reporting and
12 the other limitations I mentioned, from these data.
13 So, the incidence rates which go into a relative
14 risk calculation cannot be obtained.

15 What we can do is calculate reporting
16 rates, which is the number of reports of an adverse
17 event for the number of patients that were treated.
18 We can do that, but once we have done that and we
19 have a rate of X/100,000 patients treated per year
20 for an adverse event, then we always scratch our
21 heads and say now, what do we compare that to?
22 And, we go to the rheumatoid arthritis cohort
23 studies, for example, and when you start looking at
24 a broad array of different adverse events it
25 becomes very hard to find those data reliably

1 obtained, especially for rare events. So, it
2 becomes very hard to try to put these reporting
3 rates in perspective.

4 With the data we are going to see today,
5 because we do have two different products that are
6 used for somewhat similar indications, somewhat
7 similar products although the indications are
8 somewhat different and the products are somewhat
9 different, it is tempting to compare one to the
10 other and I think that is something that is done in
11 an exploratory way, but I think it can be very
12 hazardous to, just straight up apples and apples,
13 compare the two products' reporting rates. So, I
14 think it is very, very hazardous. It is like using
15 a chain saw, it can do a good job but you have to
16 be really careful because it can kick back.

17 [Slide]

18 Now, why is that? Because the factors
19 that are affecting the reporting, in addition to
20 the biologic factors that we are interested in
21 primarily in a true incidence of these adverse
22 events, are affected by -- as I have said a number
23 of times already and I think it is worth repeating
24 -- concomitant medications, methotrexate,
25 corticosteroids, other immunosuppressives.

1 Indications may not be the same and so that may
2 affect the patient population that is getting them
3 and their underlying risk for these adverse events.

4 The frequency of dosing -- I think if a
5 product is given more frequently, there is more
6 opportunity for a random association to occur in
7 temporal association with the more frequently given
8 product. I think that is something that is worth
9 noting. One product may be used more broadly than
10 the other, and because the patients are broader
11 they are more likely to have the adverse event.
12 That could be a factor.

13 Some products may make it easier to report
14 adverse events than other products, and that is
15 just worth considering as a possibility. Finally,
16 publicity may affect reporting. For example, this
17 meeting today may generate some publicity. We
18 don't know that, but if it does, that could affect
19 adverse event reporting to the extent any
20 particular adverse events are highlighted, or it
21 could be across the board adverse event reporting
22 being affected.

23 [Slide]

24 So, when we weigh the data we try to look
25 at the numbers of reports first of all, and that

1 directly correlates with reporting rates, and then
2 to see if there is a temporal association. A good
3 example of this was recently with the rotovirus
4 vaccine. There was a striking peak in interception
5 and a telescoping of the bowel three to seven days
6 after the vaccine was administered in infants.
7 This increased incidence really did not occur to
8 that extent at other times. So, that is a real
9 clustering in time of an adverse event and that
10 provides evidence for an association, for a causal
11 association.

12 Rechallenge means when a product is given
13 the adverse event occurs afterwards. If a product
14 is given again the adverse event occurs again.
15 That is also supporting a causal association.
16 Dechallenge is when the product is given and the
17 adverse event occurs while the product is given,
18 but then the product is stopped and the adverse
19 event goes away.

20 Unique syndromes -- I don't think we are
21 going to be seeing those today but a classic
22 example is thalidomide and phocomelia. Biologic
23 plausibility -- the products we are talking about
24 today are affecting an over-zealous immune response
25 that is resulting in disease and so it is

1 biologically plausible that a slowed down or a
2 calmed down immune system may allow, for example,
3 infections to occur more commonly. So, there is at
4 least some concern about that as a causally
5 associated type of adverse event.

6 Finally clues from clinical trials --
7 sometimes because of the size of the trials, a few
8 hundred people in some trials, you see one really
9 bad, concerning, unusual event or maybe two but
10 there are not enough to conclude that the product
11 caused these, but they are severe enough and
12 unusual enough that we can use these data in
13 addition to the MedWatch data, the passive
14 surveillance data, to say, yes, these are
15 consistent in what they are showing us.

16 Finally, analogy just means if one product
17 is shown to be causally associated with an adverse
18 event, then another product of the same type could
19 at least be suspected of having that same kind of
20 adverse event.

21 [Slide]

22 Finally, what can we do when we have real
23 strong concerns about an adverse event being
24 associated with a product? Kind of our tool box --
25 and you will hear a lot about this today -- is

1 revision to the label. But that is a step that has
2 some impact but not always as great as one would
3 want. Further steps include sending what used to
4 be called a "dear doctor" letter, now a "dear
5 healthcare professional" letter. Medication guides
6 are a form of direct to the patient teaching and
7 information, risk communication to the patient.
8 This is a newer modality, risk communication, and
9 an even more active approach is a risk management
10 program which involves more active attempts to
11 modify behavior and to educate to increase product
12 safety.

13 This is not the complete list of options
14 that we have, obviously. Research communications
15 and presenting at meetings like this I think is a
16 very good way to get the word out about concerns
17 about adverse events or concerns and things we can
18 do to prevent those adverse events. As well, we
19 have presented some of the data on infections at
20 the American College of Rheumatology meeting in
21 Philadelphia, last fall. Similarly, we can publish
22 in peer reviewed scientific journals and try to get
23 the word out that way.

24 So, I believe that is all I have today for
25 you and I am going to turn this over to Dr. Lee,

1 Dr. Jong Lee, and he is going to present some of
2 the data and some of the label changes that have
3 happened since licensure of these products. Thank
4 you.

5 **Safety Data**

6 DR. LEE: Good morning.

7 [Slide]

8 My name is Jong Lee, and I will pick up
9 from where Dr. Braun left off and continue on with
10 the topic of infections and then, more
11 specifically, with tuberculosis and other
12 opportunistic infections, particularly for
13 infliximab.

14 [Slide]

15 Backing off to both products, I will start
16 with etanercept first and I will start with the
17 original labeling. When the product was first
18 approved in November of 1998, the warning section
19 of the label was simply limited to this one
20 sentence: Administration of Enbrel should be
21 discontinued if a patient develops a serious
22 infection. There was also a precautionary
23 statement about the anti-TNF therapy of how it
24 modulates immunity and, therefore, might predispose
25 to other infections and other processes involving

1 immunity, such as malignancies.

2 [Slide]

3 Shortly after approval, in early 1999,
4 reports of serious infections, some fatal, were
5 received post-licensure for etancercept and the
6 received reports included several readily
7 recognizable risk factors, namely, diabetes
8 mellitus, active infections and history of chronic
9 infections. So, in response to this, although the
10 number of reports received were few, a bold warning
11 was added to the etancercept label.

12 [Slide]

13 I am not going to read the entire bold
14 warning, but simply point out that the warning
15 section was significantly expanded to warn of
16 serious infections, particularly in patients with
17 underlying disease which might predispose them to
18 infections, and that these patients ought to be
19 monitored closely.

20 [Slide]

21 Particular attention was drawn to the fact
22 that patients with chronic or localized infections
23 should be carefully watched and that physicians
24 should exercise caution.

25 [Slide]

1 If you notice, the two products are color
2 coded just to make sure that you stay in tune with
3 what I am saying because I will be jumping back and
4 forth between the two products as we are
5 progressing topically through different adverse
6 event categories. So, this is infliximab. In an
7 analogous fashion, in the original infliximab
8 labeling, when it was approved in October of 1998,
9 there was no bold warning section and the
10 precautionary statement about infliximab was
11 limited to a similar statement included for the
12 etancercept labeling for TNF-alpha blockade
13 therapy.

14 [Slide]

15 Reports of serious infections were also
16 received for infliximab, and these also included
17 some fatal ones, and warning was, likewise,
18 included for infliximab labeling.

19 [Slide]

20 Here, one of the reports actually had some
21 indication that it might be associated with
22 tuberculosis. The numbers were very few but the
23 actual language for infliximab warning that was
24 crafted differed slightly from that of the
25 etancercept labeling. So, it included serious

1 infections, including sepsis and disseminated
2 tuberculosis.

3 [Slide]

4 It called attention to similar types of
5 underlying conditions that might predispose them to
6 such serious infections, including
7 immunosuppressive therapy. In general, the overall
8 tone was of watching out for unknown infections in
9 the setting of limited data that is just beginning
10 to be received through post-licensure experience.

11 [Slide]

12 To make a few statements about
13 tuberculosis and infliximab, in the original
14 clinical trial data evaluating infliximab there
15 were no TB cases that were seen among 88 control
16 patients. One case of TB that was fatal was seen
17 among the 340 patients treated with infliximab and
18 methotrexate. In early post-licensure reports that
19 were received at the FDA, as of June of 2000, there
20 were 17 cases, including two fatalities; 11 were
21 European and 6 were from the United States. All of
22 these cases occurred within 2 to 4 months of
23 starting therapy.

24 [Slide]

25 The initial bold warning that was added to

1 infliximab labeling was then revised to include
2 this statement on the basis of the early
3 post-licensure experience: Patients should be
4 evaluated for the risk of tuberculosis, including
5 latent tuberculosis. Treatment for tuberculosis
6 should be initiated prior to treatment with
7 infliximab.

8 [Slide]

9 Now, at this point I would like to just go
10 over the broad overview in terms of the number of
11 patients treated and the number of MedWatch reports
12 that were received before commenting further about
13 tuberculosis. Since approval in October of 1998
14 and through March of 2001, over a 29-month period,
15 the number of patients treated with infliximab are
16 shown here and these figures are estimates by the
17 manufacturer. Worldwide, 147,000 patients
18 approximately were treated with infliximab, of
19 which 82 percent were U.S. patients and 18 percent
20 were foreign patients.

21 [Slide]

22 In terms of parallel MedWatch reporting
23 experience, from October of '98 through August of
24 2001, which is a 34-month period -- these numbers
25 are based on the FDA's database adverse event

1 reporting system -- the total number of reports
2 received for infliximab is approximately 2300, of
3 which approximately 26 percent is about infections.

4 [Slide]

5 Now let me bring you back to tuberculosis
6 and infliximab. By May of 2001, 70 cases were
7 received post-licensure, and 64 percent of these
8 came from Europe; 23 percent were U.S. and 13
9 percent from other. Most of these cases were
10 extrapulmonary and about a quarter of the cases
11 were described as disseminated tuberculosis. The
12 diagnosis of tuberculosis was frequently not
13 considered initially which delayed treatment.

14 [Slide]

15 As of August 16, 2001, yesterday, we have
16 92 cases according to our database in the adverse
17 event reporting system.

18 [Slide]

19 To comment a bit further about the
20 characteristics of these 70 reports through May 15,
21 2001, the age range went from 18 to 83 years old,
22 with a median of 57 years of age. Weeks to
23 symptoms ranged from 1 week to 52 weeks, with a
24 median of 12 weeks. The number of doses went from
25 1 to 9 doses, with a median of 3 doses.

1 Concomitant immunosuppressive therapy was given in
2 77 percent of these patients. I believe 2 of the
3 70 reports described recent exposure to
4 tuberculosis, for approximately 3 percent.

5 [Slide]

6 So, what do these numbers mean? This is a
7 table which is a bit busy but I will walk you
8 through it. On the left-hand column is the
9 MedWatch reporting rate for tuberculosis in
10 infliximab recipients. Bear in mind that these are
11 simply reporting rates, and these figures are given
12 as the numbers shown per 100,000 person years. In
13 the right-hand column are the literature TB
14 incidence estimates and these are also given as a
15 number per 100,000 person years. The first row is
16 the U.S. general population. The second row is the
17 U.S. patients with rheumatoid arthritis. The third
18 row is the U.S. patients with Crohn's disease.
19 This is not applicable here so let's jump to this
20 number first.

21 For U.S. patients with rheumatoid
22 arthritis who were given infliximab therapy, the
23 MedWatch reporting rate for tuberculosis is
24 24/100,000 person years. How does that compare
25 with some incidence estimates? There are really no

1 good figures as a comparative control. The TB
2 incidence estimate in a similar cohort would be --
3 you could say that it is simply based on one case
4 described by Wolfe et al., and being only one case
5 one cannot make much statement about that but as a
6 point estimate you could say that this is 6/100,000
7 person years. If you expand that to just the
8 general population, according to the Centers for
9 Disease Control 1999 data, it is also 6/100,000
10 person years. I believe we have a representative
11 from CDC here today who can comment more about more
12 recent data, from year 2000, which I am told is a
13 bit lower than this.

14 In terms of our reporting rate in U.S.
15 patients with Crohn's disease, the number was
16 9/100,000 person years and a comparable incidence
17 estimate for TB in that group of patients is simply
18 not available. I should comment that these figures
19 are derived based on first year of patient
20 follow-up. So, that is the TB story. It is
21 difficult to make firm conclusions, but that is the
22 data.

23 [Slide]

24 What about other opportunistic infections?
25 Well, through June of 2001 these infections caught

1 our attention. There were 9 cases of
2 histoplasmosis, including 1 fatality; 11 cases of
3 listeriosis, including 4 fatalities; and 10 cases
4 of pneumocystis pneumonia, including 3 fatalities.

5 [Slide]

6 Since the numbers are small and since
7 they appear somewhat similar to each other, I
8 presented the limited amount of data for
9 histoplasmosis and listeriosis in the same slide.
10 Again, an N of 9 for histoplasmosis, 11 for
11 listeriosis. The age range for histoplasmosis is
12 shown here, with a median of 45 years of age. That
13 compares with 67 years of age for listeriosis.
14 Median time to event was 8 weeks for
15 histoplasmosis, 10 for listeriosis; 3 doses for
16 histoplasmosis and 2 doses median for listeriosis.
17 All cases of histoplasmosis were confirmed by
18 tissue biopsy. In fact, in almost all of these
19 patients the diagnosis was kind of stumbled upon
20 after being forced to resort to a tissue biopsy
21 upon workup of an unknown infection. All cases of
22 listeriosis were diagnosed, as you might expect, by
23 culture. Concomitant steroids or methotrexate
24 therapy was given in all of these cases, which
25 confounds our analysis.

1 [Slide]

2 This is a map just to make one point.
3 Shown in grey contours here and in darker grey
4 contours there are a representation of the areas
5 that are considered to be endemic for
6 histoplasmosis in the United States. Shown on top
7 of that are these red circles which denote the
8 locations from which histoplasmosis on infliximab
9 therapy originated. As you note, the scatter of
10 these red dots roughly coincides with what we
11 expect with histoplasmosis endemic areas. These
12 states are shown here, Alabama, Indiana, Iowa,
13 Kentucky, Louisiana, two from Ohio, two from
14 Tennessee and one from Wisconsin.

15 [Slide]

16 That is the histoplasmosis and listeriosis
17 story. What about pneumocystis pneumonia? We have
18 10 reports, with a median age of 57 with a range of
19 15 through 69. Week to symptoms, 4 weeks with a
20 range of 1-9. Again, concomitant steroids are
21 methotrexate therapy in all cases.

22 [Slide]

23 So, based on all of this data about
24 opportunistic infections and TB, the warning label
25 for infliximab is under revision as we speak, and

1 the manufacturer, Centocor, has been working with
2 the FDA very closely and extensively, and this is
3 the current version of the proposed box warning,
4 and your comments will be welcome about the wording
5 of this proposed box warning.

6 I will simply read this to you:
7 Tuberculosis (frequently disseminated or
8 extrapulmonary at clinical presentation), invasive
9 fungal infections and other opportunistic
10 infections have been observed in patients receiving
11 Remicade. Some of these infections have been
12 fatal. Patients should be evaluated for latent
13 tuberculosis infection with a tuberculin skin test.
14 Treatment of latent tuberculosis infection should
15 be initiated prior to therapy with Remicade.

16 That is what is typically referred to as
17 the black box warning, but there is also the plain
18 warning section that is also proposed, and this is
19 the proposed language: Cases of histoplasmosis,
20 listeriosis, pneumocystis and tuberculosis have
21 been observed in patients receiving Remicade. For
22 patients who have resided in regions where
23 histoplasmosis is endemic, the benefit from risks
24 of Remicade treatment should be carefully
25 considered before initiation of Remicade therapy.

1 [Slide]

2 This slide is simply to trigger some
3 discussion later on, but just to point out that TNF
4 infliximab is a monoclonal antibody directed
5 against TNF-alpha, and in vitro lysis of monocytes
6 and macrophages has been shown with infliximab for
7 cells expressing transmembrane TNF-alpha, and these
8 elements of the cell-mediated immunity have been
9 known to be important for these infections in the
10 literature, and post-licensure experience has been
11 consistent with that. Again, this is simply to
12 serve as a discussion point.

13 [Slide]

14 At this point I will turn it over to Dr.
15 Jeffrey Siegel, who will proceed with TB and other
16 opportunistic infections for etancercept, as well
17 as many other post-licensure adverse events.

18 **TB and Other Opportunistic Infections**

19 DR. JEFFREY SIEGEL: Thank you, Jong.
20 Good morning, ladies and gentlemen. As the agency
21 became concerned about reports of tuberculosis on
22 anti-TNF therapy, the agency reviewed all the
23 available data on occurrence of tuberculosis in
24 patients receiving etancercept.

25 [Slide]

1 We reviewed the clinical trial data which
2 showed the following: At the time of consideration
3 of a label change for tuberculosis with
4 etancercept, no cases of tuberculosis had been
5 observed in patients treated in clinical trials.
6 This included 1260 subjects in European trials, 14
7 of whom had a history of tuberculosis and, in
8 addition, 2024 subjects had been treated in U.S.
9 trials with no cases of tuberculosis. This
10 included 5 with a history of tuberculosis and 7 who
11 were later found, in retrospect, to have been PPD
12 positive at baseline. Subsequent to the label
13 change, one fatal case of disseminated tuberculosis
14 has been observed in an elderly man in a congestive
15 heart failure trial in Europe.

16 [Slide]

17 We also reviewed the post-licensure
18 adverse event reports that had been received.
19 Again, at the time of the label change, in the year
20 2000 a total of 5 cases had been received. Three
21 of these occurred in patients receiving etancercept
22 in Europe and 2 of the cases occurred in the U.S.
23 We reviewed the individual case reports on the
24 patients developing tuberculosis in the U.S., and
25 both of these patients had established risk factors

1 for tuberculosis.

2 One of the patients had recent exposure to
3 active tuberculosis from a family member that they
4 were caring for who was later found to have active
5 TB. The other patient had extensive foreign travel
6 to areas endemic for tuberculosis. The five cases
7 of tuberculosis occurred at varying times after
8 initiation of etancercept therapy.

9 Looking at the total number of reports
10 that had been received and the total number of
11 patients who received etancercept at that time
12 indicated that the reporting rate for tuberculosis
13 did not exceed the U.S. rates estimated at 5-8
14 cases/100,000 patient years.

15 [Slide]

16 Based on this information, the following
17 change was made to the etancercept label. The
18 information was added to the bold warning in the
19 Enbrel label as follows -- the following statement
20 was added: Rare cases of tuberculosis have been
21 observed in patients treated with TNF antagonists,
22 including etancercept.

23 [Slide]

24 The agency also reviewed other
25 opportunistic infections that had been seen in

1 patients receiving etancercept. At the time of the
2 label change that was made regarding opportunistic
3 infections, 11 cases had been reported to the
4 agency. This is as of August 2000. Many of these
5 cases were in patients who had clearly identifiable
6 risk factors for opportunistic infections,
7 including patients receiving high doses of
8 corticosteroids, patients receiving cytotoxic
9 therapy, and patients with other debilitating
10 diseases.

11 [Slide]

12 Based on these 11 cases, the following
13 change was made to the Enbrel label -- the
14 following statement was added to the adverse
15 reaction section of the label: In post-marketing
16 experience infections have been observed with
17 various pathogens, including viral, bacterial,
18 fungal and protozoal organisms. Infections have
19 been noted in all organ systems and have been
20 reported in patients receiving Enbrel alone or in
21 combination with immunosuppressive agents.

22 [Slide]

23 To put the number of cases of adverse
24 events into some perspective, I want to briefly
25 review the number of patients who have been treated

1 with etancercept worldwide. Worldwide, the number
2 of patients treated is estimated at approximately
3 102,000. In the U.S., 96,000 patients have been
4 treated, representing 94 percent of the worldwide
5 experience. Outside of the U.S., 6000 patients
6 have been treated, or 6 percent of the overall
7 experience.

8 [Slide]

9 The agency has received 18,500 MedWatch
10 adverse event reports for etancercept in the 33
11 months since etancercept was approved, in November
12 of 1998. I want to point out there are a number of
13 things that may contribute to the number of
14 MedWatch reports that have been received, and I
15 think the sponsor may be discussing this later in
16 their presentation. One thing that they have
17 proposed as a possible explanation is a facilitated
18 reporting system that they have implemented, but
19 this is just one consideration. The fraction of
20 reports that represent infections is 22 percent.

21 [Slide]

22 The number of opportunistic infections as
23 of the current time is shown on this slide. Three
24 cases of cryptococcosis have been reported; 1 case
25 of histoplasmosis; 5 cases of pneumocystis

1 pneumonia that I will show you in more detail in
2 the next slide; 1 case of listeriosis; 1 of
3 Mycobacterium avium intracellulare; 1 case of
4 Mycobacterium kansasii; 1 of a CMV pneumonitis; and
5 1 case of herpes encephalitis.

6 [Slide]

7 As I mentioned, 5 cases of Pneumocystis
8 carinii pneumonia have been reported. The median
9 age of these patients was 56, and the time to
10 developing symptoms was 9 weeks after initiation of
11 etancercept therapy. Obviously, other concomitant
12 medications can play a role in the development of
13 pneumocystis, and I will note that 4/5 cases were
14 also on concomitant corticosteroids or
15 methotrexate.

16 [Slide]

17 In the year 2000 the agency became aware
18 of a number of reports of demyelinating disease. I
19 am just switching topics here as I will be doing
20 through the rest of my presentation. The agency
21 became aware of reports of demyelinating disease
22 occurring in patients receiving etancercept. At
23 the time of the label change that was added to the
24 etancercept label for this adverse event, 10 cases
25 had been reported. At the current time, I believe

1 it is 17 cases.

2 These 10 cases are reported in a
3 publication which is in press in Arthritis and
4 Rheumatism. I will just review some of the
5 characteristics of these cases. These cases were
6 reviewed by several neurologists and it was
7 concluded that two of the cases were consistent
8 with new onset of multiple sclerosis. These
9 patients had a variety of signs and symptoms
10 including paresthesias, spasticity and changes on
11 MRI that were consistent with multiple sclerosis.
12 Two cases were consistent with exacerbation of
13 preexisting or established multiple sclerosis.

14 In addition, two of the cases had a
15 variety of neurologic symptoms but it also included
16 altered mental status, which is not generally
17 considered characteristic of MS, at least not in
18 the early presentation. One of these patients had
19 muscle rigidity eventually requiring intubation.
20 The other presented with difficulty with writing.
21 These cases were considered so severe and of
22 uncertain etiology so that a brain biopsy was
23 obtained. In one case spongiotic changes were
24 seen; in the other case demyelination was seen. In
25 the other cases of possible demyelinating disease,

1 these cases had features consistent with multiple
2 sclerosis but did not meet the diagnostic criteria
3 for multiple sclerosis.

4 As of the spring of 2001, 18 cases have
5 been reported on etancercept. A quarter of these
6 cases were in patients receiving concomitant
7 methotrexate. I just want to mention that Evelyn
8 Edwards, in our post-marketing group, worked on
9 pulling this data together.

10 [Slide]

11 The outcome of the patients reported with
12 demyelinating disease is shown on this slide. All
13 the patients improved after discontinuing
14 etancercept. This is important. This is what we
15 call positive dechallenge, as Dr. Braun was talking
16 to you about as one factor to be considered in
17 assessing an association between an adverse event
18 and exposure to a drug. A few of the cases did
19 have persistent neurologic deficits. In several
20 cases etancercept was reinstated without worsening
21 of neurologic symptoms.

22 Positive rechallenge occurred in one case.
23 This was a case of a patient who had gotten better,
24 then etancercept was reintroduced and the patient
25 had a flare of the demyelinating disease.

1 Interpretation of this positive rechallenge is made
2 more complicated by the fact that corticosteroids
3 had just been tapered in this case.

4 [Slide]

5 So, based on this information, the
6 following addition was made to the etancercept
7 label, the following wording was added: Treatment
8 with Enbrel and other agents that inhibit TNF have
9 been associated with rare cases of new onset or
10 exacerbation of central nervous system
11 demyelinating disorders, some presenting with
12 mental status changes and some associated with
13 permanent disability. Rare cases of transverse
14 myelitis, optic neuritis, and new onset or
15 exacerbation of seizure disorders have been
16 observed in association with Enbrel therapy.

17 [Slide]

18 The label goes on to say that the causal
19 relationship to Enbrel therapy remains unclear.
20 While no clinical trials have been performed
21 evaluating Enbrel therapy in patients with multiple
22 sclerosis, other TNF antagonists administered to
23 patients with multiple sclerosis have been
24 associated with increases in disease activity.
25 Prescribers should exercise caution in considering

1 the use of Enbrel in patients with preexisting or
2 recent onset of central nervous system
3 demyelinating disorders.

4 Some of the information that went into the
5 wording I will discuss in subsequent slides. If
6 you have questions about other information that I
7 may not have covered, please make sure to ask me at
8 the end of the presentation.

9 [Slide]

10 As the agency became concerned about
11 demyelinating syndromes in patients receiving
12 etancercept, the issue arose about whether this
13 might be seen with other agents that inhibit tumor
14 necrosis factor. Reports of demyelinating disease
15 in patients receiving infliximab were reviewed as
16 well. Ultimately, a label change was made to the
17 Remicade or infliximab label subsequent to this
18 review. At that time, 3 cases of demyelination had
19 been seen on infliximab. Generally, review of
20 these cases showed a clinical presentation and
21 course that was similar to the cases seen on
22 etancercept. Patients presented with paresthesias,
23 weakness and MRI changes consistent with multiple
24 sclerosis. Some of these cases had preexisting
25 neurologic symptoms. A review in August of 2001,

1 at the current time, shows 5 cases in our database
2 of demyelinating disease with infliximab.

3 [Slide]

4 In crafting information that would be
5 helpful to physicians in trying to understand
6 demyelinating disease in patients receiving
7 infliximab, we looked at other evidence as well.
8 Some of you may know that animal models of multiple
9 sclerosis have shown both positive and negative
10 effects of TNF, but there were a number of studies
11 suggesting that blockage of TNF in experimental
12 models was beneficial to animals with this model of
13 multiple sclerosis.

14 So based on this, a number of
15 investigators initiated prospective clinical trials
16 of TNF blockade in patients with established
17 multiple sclerosis, and both of these reports have
18 been published.

19 One study was a randomized, double-blind,
20 placebo-controlled trial of lenercept in multiple
21 sclerosis. Lenercept is a product which is not
22 licensed. It is a soluble TNF receptor that binds
23 and neutralizes TNF. This study of lenercept in
24 patients with established multiple sclerosis showed
25 a statistically significant shortening in the time

1 to flare of multiple sclerosis and the study was,
2 therefore, stopped. This shortening in time to
3 flare was statistically significant.

4 Another study was done of TNF blockade in
5 patients with established multiple sclerosis. This
6 was done with infliximab. When the first two
7 subjects treated were evaluated, it was found that
8 both had developed worsening of their MRI lesions,
9 increased inflammatory changes in their
10 cerebrospinal fluid, but these patients did not
11 develop a clinical flare. The study was, of
12 course, stopped after these two cases were
13 reported.

14 [Slide]

15 Again, based on the information that we
16 had, the following label change was made to the
17 infliximab label: Infliximab and other agents that
18 inhibit TNF have been associated in rare cases with
19 exacerbation of clinical symptoms and/or
20 radiographic evidence of demyelinating disease.
21 Prescribers should exercise caution in considering
22 the use of Remicade in patients with preexisting or
23 recent onset of central nervous system
24 demyelinating disorders.

25 [Slide]

1 The next adverse event that I am going to
2 be discussing are cases of aplastic anemia reported
3 with etancercept. A change based on these cases
4 has already been made to the etancercept label. At
5 the time of that label change, in the year 2000,
6 two cases of aplastic anemia had been reported. In
7 addition, a third case of pancytopenia was reported
8 that was consistent with aplastic anemia but it had
9 incomplete documentation. So, I am counting two
10 cases of established documented aplastic anemia.
11 Both of these cases were confirmed with bone marrow
12 hypoplasia across all blood elements, and both of
13 these cases were, unfortunately, fatal. One
14 additional case of aplastic anemia has been
15 reported in a patient on etancercept subsequent to
16 the label change.

17 In addition, seven cases of pancytopenia
18 were found in our database. Review of these seven
19 cases showed that all of these patients were taking
20 other drugs associated with pancytopenia, including
21 cytotoxic agents and other agents that are known to
22 be associated with pancytopenia. So a conclusion
23 about an association between pancytopenia and
24 etancercept cannot be made.

25 [Slide]

1 Review of the literature for the incidence
2 of aplastic anemia in patients with rheumatoid
3 arthritis showed a number of things. First,
4 overall incidence estimates in the U.S. population
5 as a whole suggests that there are few cases per
6 one million patient years, but in patients with
7 rheumatoid arthritis estimates are somewhat higher
8 in the literature, and some reports suggest a rate
9 that is up to 8-fold higher. One obvious
10 consideration is whether other agents that are used
11 for rheumatoid arthritis may be predisposing to
12 aplastic anemia, but the investigators who wrote
13 these reports could not make firm conclusions about
14 this.

15 [Slide]

16 So the label change that was made
17 subsequent to review of these cases is as follows:
18 Rare reports of pancytopenia, including aplastic
19 anemia, some with a fatal outcome, have been
20 reported in patients treated with Enbrel. The
21 causal relationship to Enbrel therapy remains
22 unclear. Although no high risk group has been
23 identified, caution should be exercised in patients
24 being treated with Enbrel who have a previous
25 history of significant hematologic abnormalities.

1 All patients should be advised to seek immediate
2 medical attention if they develop signs and
3 symptoms suggestive of blood dyscrasias or
4 infection, for example, persistent fever, bruising,
5 bleeding, pallor while on Enbrel. Discontinuation
6 of Enbrel therapy should be considered in patients
7 with confirmed significant hematologic
8 abnormalities.

9 I want to mention one thing at this point,
10 something that I should have mentioned earlier,
11 which is that a number of cases of pancytopenia
12 have been reported on infliximab as well. Many of
13 these cases are also associated with other drugs
14 that are associated with pancytopenia.

15 In addition, I also want to note that in
16 the label change for demyelinating disease a number
17 of other disorders were mentioned, including
18 seizures, and seizures have been reported in
19 patients receiving infliximab as well.

20 [Slide]

21 Several other label changes have been made
22 to the etancercept label as well as to the
23 infliximab label. Intestinal perforation was
24 listed in the infliximab label at the time of
25 licensure but not in the etancercept label. Since

1 then rare cases have been reported of intestinal
2 perforation on both agents, and this was added as
3 an adverse event that has been seen in patients
4 receiving etancercept.

5 I should note, however, that intestinal
6 perforation has been reported to be associated with
7 rheumatoid arthritis and patients receiving
8 non-steroidal anti-inflammatory drugs as well as
9 patients receiving high dose and low dose
10 corticosteroids have also been reported to be at
11 increased risk. So, the association with TNF
12 blocking agents is unclear.

13 At the time of the original licensure of
14 infliximab several cases of lupus-like syndrome had
15 been reported in patients in clinical trials.
16 Additional cases of lupus-like syndrome have been
17 reported post-marketing with infliximab, and
18 wording advising healthcare providers and patients
19 about this was in the Remicade label.

20 Subsequent to licensure of etancercept,
21 several cases of subacute cutaneous lupus and
22 discoid lupus with autoantibodies were seen.
23 Language discussing this has been added to the
24 etancercept label as well.

25 [Slide]

1 That is all that I will be covering on the
2 label changes made with these two agents, but
3 another adverse event has come to the attention of
4 our post-marketing group, namely, lymphoma. This
5 has been a concern with other agents for rheumatoid
6 arthritis and I will be presenting to you the
7 information that we have on the occurrence of
8 lymphoma in patients receiving infliximab and
9 etancercept.

10 Shown on this slide is a description of
11 the 10 reports of lymphoma that have been received
12 in patients receiving infliximab. The median age
13 of these patients is 62 and the median time to
14 diagnosis following initiation of infliximab is 4
15 weeks.

16 In 4 of these cases concomitant
17 immunosuppressive medications were being taken.
18 Two of these cases were cases of Hodgkin's disease
19 and 8 cases were non-Hodgkin's lymphoma. I am
20 going to mention that Laurie Brown at the FDA was
21 responsible for reviewing these data.

22 [Slide]

23 Cases of lymphoma have also been reported
24 in patients receiving etancercept. A total of 18
25 reports have been received, with a median age of 61

1 and a time to diagnosis of 8 weeks.

2 Immunosuppressive medications were being taken by
3 these patients, in approximately 80 percent of
4 them. One of these cases was Hodgkin's disease;
5 the other 17 were non-Hodgkin's lymphoma.

6 I am going to turn my attention in the
7 rest of my presentation to some thoughts about our
8 interpretation of post-licensure adverse events and
9 what we can do to further characterize the safety
10 of these agents.

11 [Slide]

12 We are often in the situation of licensing
13 a biologic product or approving a drug with an
14 assessment of safety based on clinical trial data.
15 In some cases unanticipated post-licensure events
16 are reported that were not expected based on the
17 pre-approval safety database. Some of the reasons
18 that may contribute to this difference between
19 pre-marketing and post-marketing assessments are
20 shown here. Only small numbers of patients are
21 enrolled in clinical trials so rare adverse events
22 may not be seen. However, another contributing
23 factor may be the different use of products in
24 clinical trials pre-marketing and post-licensure.

25 Some of those are shown here and include

1 different patient populations that are treated.
2 Oftentimes concomitant medications are different in
3 patients in clinical practices who are exposed
4 post-marketing compared to very controlled
5 circumstances in clinical trials. Patients may be
6 treated who have concurrent medical conditions that
7 may predispose to certain adverse events
8 post-marketing, who are excluded from clinical
9 trials. Finally, there is often a practice of
10 trying higher doses than the recommended doses
11 post-marketing, and use of higher doses in some
12 cases may also predispose to adverse events that
13 weren't expected pre-marketing.

14 [Slide]

15 One approach to getting further
16 information about safety than that which is
17 available in the usual clinical trials is to
18 conduct additional safety studies. These can be
19 carried out either pre-marketing or post-marketing
20 and each may well have a role. These studies can
21 address special populations, including populations
22 considered at increased risk; varying doses that
23 may better represent the doses that may be given
24 post-marketing; and safety in settings closer to
25 those of actual practice and differing from those

1 which are in play during clinical trials.

2 [Slide]

3 The timing of these safety studies may
4 differ from one agent and one situation to another.
5 For agents that are being considered that represent
6 a significant advance over currently available
7 therapies, in some cases the public health needs
8 may require rapid approval of these agents. For
9 agents that are not addressing an unmet medical
10 need, more thorough exploration of safety may be
11 warranted pre-approval. It is the practice of the
12 division where I work, the Division of Clinical
13 Trials at the Center for Biologics, to encourage
14 pre-approval randomized safety studies for new
15 agents that are being considered for use in
16 patients with rheumatoid arthritis.

17 [Slide]

18 Now I will go on to talk about several of
19 the safety studies that are currently ongoing. At
20 the time of licensure of Enbrel, Immunex agreed to
21 conduct a long-term safety study. This is a 3-year
22 open-label study of 1200 patients receiving Enbrel.
23 The objectives of this study are to assess
24 long-term safety, including mortality rate,
25 incidence of malignancy in autoimmune disease and

1 compare that to historical control databases.

2 [Slide]

3 In addition, after receipt of the
4 post-marketing reports of serious infections,
5 Immunex has also begun a safety study of use of
6 etancercept in patients who may be at increased
7 risk of serious infections. This study is a 1000
8 patient randomized, 4-month, double-blind,
9 placebo-controlled study of Enbrel in patients with
10 active rheumatoid arthritis who may be at increased
11 risk of infection, including the following
12 categories, patients with diabetes mellitus
13 requiring insulin or oral hypoglycemic agents;
14 patients with chronic pulmonary disease, including
15 chronic obstructive pulmonary disease or asthma;
16 patients with recurrent bronchitis, sinusitis or
17 urinary tract infections, at least two in the past
18 year; or history of pneumonia in the past year.
19 Their statistical plan indicated that there was 94
20 percent power to exclude a 2-fold relative risk of
21 serious infection with use of etancercept based on
22 95 percent confidence intervals.

23 [Slide]

24 Centocor has also begun a Phase IV
25 post-marketing safety study. This study is a

1 1-year randomized, placebo-controlled trial of 1000
2 patients receiving background methotrexate. The
3 design is as follows, the study drug, Remicade,
4 will be given intravenously at 0, 2, 6 and 14 weeks
5 and then will be given every 2 months. In the
6 first group, they will be started on placebo
7 through week 14 and then they will receive the
8 recommended starting dose of infliximab, namely 3
9 mg/kg, throughout the rest of the trial. The
10 second group will receive the recommended starting
11 dose of infliximab, 3 mg/kg, through week 14, then
12 increased by 1.5 mg/kg to a maximum of 9 mg/kg.
13 The third group will start and continue on
14 infliximab 10 mg/kg.

15 [Slide]

16 This study allows a variety of additional
17 DMARDs to be used, again as I mentioned before, to
18 be closer to clinical practice. The primary
19 endpoint of the study is the incidence of serious
20 infections over one year, and it is estimated that
21 the study has 80 percent power to detect a 2-fold
22 increase in serious infections.

23 [Slide]

24 In conclusion of this part of the
25 presentation, a variety of rare, serious adverse

1 events have been reported with the licensed a-TNF
2 agents. Some of these appear possibly related to
3 inhibition of host defenses. Other of these
4 serious adverse events were unexpected.

5 Overall, the post-marketing experience
6 still suggests a favorable risk/benefit ratio for
7 use of these agents. Safety studies pre- and
8 post-marketing may clarify the safety of TNF
9 antagonists and identify strategies to minimize
10 serious adverse events.

11 I will now turn the podium over to Dr.
12 Schwieterman for some concluding remarks.

13 Concluding Remarks

14 DR. SCHWIETERMAN: Thank you, Jeff. I
15 don't have any slides but wish, rather, to list
16 some of the people that have been involved at least
17 in the basic review work. It has involved a close
18 collaboration between the Office of Therapeutics
19 and the Office of Biostatistics and Epidemiology.
20 Some of the names you have heard already, Michelle
21 Gershon, Ms. Evelyn Edwards, Dr. Albert Weis, Dr.
22 Matinu, Dr. Laurie Brown, Dr. Carolyn Makofsky from
23 the Office of Biostatistics, obviously Dr. Siegel,
24 and Dr. Barbara Matthews who was involved in some
25 of the earlier label changes.

1 We have presented here a very broad and
2 large number of label changes and types of adverse
3 events, and we will hear soon from the sponsors
4 about their perspective and then, I hope, have a
5 discussion about some of these issues. So, that
6 concludes our data presentation or update, and with
7 most of the staff here, we are happy to clarify or
8 answer any questions.

9 DR. WILLIAMS: Any specific questions the
10 panel has for the FDA?

11 DR. ABRAMSON: Actually, I have one
12 comment and then a question. I would like to
13 congratulate, in fact, the FDA for this process
14 over the time since licensing of these agents
15 because this committee was concerned in 1998 that
16 we knew we had an effective new therapy but there
17 was great concern over the long-term toxicity, and
18 I think the system you have put in place and the
19 means by which you have captured this information
20 is impressive and I think reassuring that the
21 system is, in fact, working in post-marketing
22 surveillance.

23 I just have one clarification I think for
24 Dr. Siegel. In the etancercept opportunistic
25 infection, there are 4 atypical mycobacterium

1 infections I think, and I wasn't sure whether those
2 were in addition to the 5 cases that appeared on an
3 earlier slide of TB or whether that was 5
4 mycobacterium tuberculosis and then 4 atypicals.

5 DR. JEFFREY SIEGEL: Yes, these were
6 additional cases. The discussion of tuberculosis
7 was specifically mycobacterium tuberculosis and did
8 not include the atypical infections.

9 DR. WILLIAMS: Any further specific
10 questions for the FDA? Dr. Katona?

11 DR. KATONA: Looking at the tables and the
12 age groups which are indicated, there is only one
13 in infliximab that was an 11-year old where it
14 started. Could you please share with us whether
15 there have been any adverse reactions in the
16 pediatric populations? Anything else in particular
17 in the children?

18 DR. JEFFREY SIEGEL: Gosh, I am not sure I
19 reviewed all this specifically from that point of
20 view. I can tell you that one of the cases of
21 tuberculosis with etancercept was a child. Perhaps
22 the sponsor can tell me the exact age, and it was
23 of the ankle.

24 SPONSOR: It was a 9-year old child.

25 DR. JEFFREY SIEGEL: Nine-year old child

1 apparently. I don't recall noting that other
2 events were in children.

3 DR. KATONA: Thank you.

4 DR. WILLIAMS: Any further questions? If
5 not, we will move on to the open public hearing.
6 We have four people who have registered for the
7 open public hearing. We would ask them also to
8 identify any financial interests they have in
9 either of the products being discussed or any
10 others that they may wish to discuss. The first
11 one is Judith Levinson.

12 **Open Public Hearing**

13 MS. LEVINSON: Good morning, Mr. Chairman
14 and members of the Food and Drug Administration.
15 My name is Judith Levinson. I am 57 years old, an
16 individual who has suffered from rheumatoid
17 arthritis for 17 years. I have been on the drug
18 Enbrel since January 7th, 1999 and have
19 administered approximately 274 shots. I am not a
20 paid spokesperson, but I do own stock in Immunex,
21 having purchased it two weeks after I began
22 treatment because I had such confidence and faith
23 in this drug and this company.

24 Some of you might remember me from the
25 April 11th, 2000 meeting. At that time, I told you

1 about my 13 surgeries that I had undergone to
2 correct hand, wrist and foot deformities caused by
3 severe RA. I was asking for your approval for
4 newly diagnosed patients to have the opportunity to
5 receive Enbrel as part of their treatment. I
6 applaud you for making this decision that has made
7 this possible.

8 Today I am here to discuss a different
9 issue, the review of Enbrel to determine if it is
10 safe. These ongoing reviews of new breakthrough
11 drugs are essential to protect all individuals from
12 potential harmful side effects. Several months ago
13 I was taking a drug for an unrelated problem.
14 After your careful review, this drug was recalled
15 from the shelves of pharmacies because of potential
16 risk and complications. I found out about this
17 recall from the news media and from reading the
18 newspaper. I was never notified by the
19 manufacturer or the drug company.

20 Enbrel has been a miracle drug for me. It
21 has given me my life back. Before I began taking
22 Enbrel I visualized myself being in need of
23 constant help even to do the simplest thing. But
24 not now. Enbrel has restored my strength and
25 stamina, allowing me to forego my afternoon naps,

1 giving me the energy to make dinner for my family.
2 Today I am a productive individual, a wife, mother,
3 sister, daughter. I am a published poet and have
4 designed stained glass panels. Recently I have
5 begun a new hobby, working with fusible glass to
6 make jewelry, plates and wall hangings.

7 Over the years of my illnesses, I have
8 taken many prescribed drugs, some of which have
9 caused severe side effects, including nausea, fluid
10 retention, puffiness, stomach distress and
11 headaches, to name a few. I am happy to say that
12 with Enbrel I have not experienced any of these.
13 To my knowledge, other drug manufacturers do not
14 notify their users about possible dangers to the
15 extent that is being done today by companies like
16 Immunex and Wyeth-Ayerst. Through advertisement in
17 "The New York Times" newspaper, the Arthritis
18 Magazine Today, the ENLIVEN support group, through
19 e-mail, through literature accompanying each box of
20 Enbrel, and also with each prescription from the
21 pharmacy, every effort is being made to keep
22 patients aware of signs to look for which may
23 indicate a problem.

24 Several years ago I was barely able to
25 hold a fork, while today I am able to hold tweezers

1 to pick up small pieces of glass. Enbrel has
2 reduced the fatigue, swollen joints and incredible
3 pain that I had before starting this miracle drug.
4 Immunex and Wyeth-Ayerst are diligent in keeping
5 their patients informed about any new findings
6 regarding Enbrel. I have every confidence that
7 Enbrel is safe and that if any problems should
8 arise I will be notified immediately to contact my
9 doctor.

10 During my routine lab work, taken November
11 12th, 1998, it indicated that there were eight
12 levels either higher or lower than they should be.
13 I am happy to tell you that for months my lab work,
14 last taken July 10th, 2001, shows that all my
15 levels are within the normal range. Enbrel has
16 made this possible. Thank you for allowing me to
17 speak to you today.

18 DR. WILLIAMS: Thank you for your return
19 visit to the committee. The next person is Joan
20 London.

21 MS. LONDON: Good morning. My name is
22 Joan London, and I would like to thank the Food and
23 Drug Administration and the Arthritis Advisory
24 Committee for this opportunity to speak to you
25 today.

1 I have rheumatoid arthritis and I am here
2 as a private citizen, with no affiliation with
3 either of the drug companies. I do serve on the
4 Board of Directors of the Maryland Chapter of the
5 Arthritis Foundation, and I am a member of the
6 organization's National Public Policy and Advocacy
7 Committee. However, I appear before you today on a
8 personal level to share my story as a 57-year old
9 woman who has lived with rheumatoid arthritis for
10 31 years, since I was 26 years old. I am also a
11 patient taking Enbrel injections twice a week. I
12 am here to describe what my life was like prior to
13 Enbrel, and the health and quality of my life now,
14 which is considerably improved.

15 The purpose of this hearing is to review
16 the safety of the new biologic modifiers for
17 rheumatoid arthritis. Therefore, I want to
18 emphasize right up front that in 15 months of
19 Enbrel injections I have had no complications.
20 None. In fact, the quality of my life continues to
21 improve daily. I do get occasional bruising around
22 the injection site and once in a while the site
23 bleeds a tiny bit after the injection. It is
24 obviously no fun to have an injection twice a week.
25 But these annoyances are a very, very small price

1 to pay for a medication that has apparently
2 eliminated the red, hot and painful joints in my
3 body, improved my mobility and reduced my pain and
4 disability. As you see, I got up out of a chair
5 and walked up to see you.

6 To appreciate how far I have come since I
7 started on Enbrel in June 2000, we need to step
8 back to the time preceding my first Enbrel
9 injection. After 29 years of fighting the battle
10 of living with rheumatoid arthritis, the disease
11 had ravaged my body. Despite the use of every
12 treatment modality to date, including methotrexate
13 and most recently Arava, the joints and surrounding
14 areas throughout my body were hot, swollen, painful
15 and deformed. In 1995, I had to go on long-term
16 disability, leaving a successful career, to have
17 reconstructive surgery on both hands and wrists.
18 Barely recovered from these surgeries, in August,
19 1999, I had to have life-saving spinal fusion
20 surgery of C1, 2, 4 and 5. The arthritis had eaten
21 away at the surrounding joints and my spinal cord
22 had become unstable.

23 I survived this surgery but my body was
24 exhausted and the rheumatoid arthritis ravaged on.
25 In February 2000, I developed either an allergic

1 reaction to Arava or codeine and had to discontinue
2 all medications except methotrexate and steroids.
3 Going off the anti-inflammatory drugs and pain
4 medicines left me helpless to fight the pain and
5 stiffness of the severe RA symptoms. I went into a
6 total body flare up. Every joint hurt. Every
7 movement was agony. The flare up became so
8 exacerbated that I needed a wheelchair. A friend
9 had to move in and help me with the tasks of daily
10 living, and I have never felt so much pain in my
11 life -- not from several kidney stone attacks or
12 labor pains of three children. Someone had to
13 dress me and I almost could not bend my elbows to
14 raise my hands to my mouth to feed myself. The
15 quality of my life was horrific and I was terribly
16 frightened that I would remain like this.

17 Enter Enbrel into my life! Up to this
18 point I had not tried Enbrel because of the cost.
19 As a patient with Medicare coverage for long-term
20 disability, I had no prescription drug coverage.
21 In June 2000, my courageous and caring
22 rheumatologist, Dr. Robert Bunning, Director of
23 Rheumatology at the National Rehabilitation
24 Hospital in Washington, D.C., said he had watched
25 me suffer long enough. We would work out the

1 payment; I needed treatment fast and Enbrel was our
2 best hope.

3 I received an Enbrel injection on June 7,
4 2000. I also received a huge steroid injection to
5 try to calm the severe flare up. Three days later
6 I received another Enbrel injection and another
7 steroid injection. The next day I began to feel
8 some relief. Within 10 days the flare up began to
9 subside. I was out of the wheelchair in less than
10 two weeks, and able to perform personal tasks like
11 eating and dressing myself. In two weeks I could
12 live alone again.

13 For the next 12 weeks I remained on 10 mg
14 of prednisone, 10 mg of methotrexate and 2 Enbrel
15 injections a week, along with anti-inflammatory and
16 pain medicines. As the weeks passed, the red,
17 swollen joints miraculously became smaller, less
18 hot, less painful. I also began to notice
19 increased joint mobility that I hadn't had in a
20 long time, in some cases in years, like lifting my
21 arm to the top of my head to comb the back of my
22 hair.

23 By September 2000, just three months after
24 beginning Enbrel, I was back to the functional
25 level I experienced prior to the flare up. I was

1 now able to slowly taper my steroid dosage. In
2 January 2001, I took my last prednisone pill. In
3 March 2001, I felt so well that I decided to try
4 and reduce my methotrexate dose. I had been on
5 this drug for 15 years and was concerned about side
6 effects. Moreover, I believe in my case
7 methotrexate had not arrested the disease at all.
8 In June 2001, I took my last methotrexate pill.
9 Currently, I remain on two Enbrel injections a
10 week, the anti-inflammatory medication Arthrotec
11 and pain medicine.

12 I keep a journal where I record my
13 arthritis symptoms and the location of each Enbrel
14 injection -- stomach, thigh or arm. Yesterday I
15 received my 126th injection into my right arm --
16 well, total -- but the injection yesterday was into
17 my right arm. I am very pleased to report that I
18 have never experienced a complication from Enbrel,
19 and the disease is becoming more and more harnessed
20 and I am feeling stronger and better all the time.

21 Am I totally pain and symptom free? No.
22 My knees remain painful and my left hip hurts all
23 the time. However, x-ray findings demonstrate that
24 these problems are from damage caused prior to
25 receiving Enbrel. The really good news is that the

1 rest of my joints and surrounding areas have
2 responded totally to Enbrel. There are no swollen
3 or hot joints in my body except for my knees.

4 Enbrel is a new medication and I know that
5 this committee is assessing its use. Receiving an
6 injection twice a week involves a commitment of
7 time, expense and some degree of discomfort from
8 the shot itself. I am here to tell you it is worth
9 it.

10 Never, never in my wildest dreams did I
11 expect to testify before the Arthritis Advisory
12 Committee of the Food and Drug Administration,
13 especially about something as personal as my
14 30-plus years of living with rheumatoid arthritis.
15 The irony here is that for at least the first 20
16 years following my disease diagnosis I attempted to
17 hide it from employers, family and friends alike,
18 frightened that I would lose my job and way of life
19 if people knew how the disease was affecting me.
20 But it is time to speak out about the new biologic
21 medications and the help and the hope that they
22 offer people with rheumatoid arthritis. That is
23 why I stand before you today, and I mean stand as
24 opposed to lean on a walker or cane, sit in a
25 wheelchair or speak to you lying down from a

1 stretcher.

2 My dear departed mother, Adele London,
3 also suffered courageously from rheumatoid
4 arthritis. Her father, my grandfather Louis
5 Selenkow, also had rheumatoid arthritis, in past
6 years called "the rheumatism." Other family
7 members, including aunts and cousins, have suffered
8 and endured this awful disease. For the 2.5
9 million Americans with rheumatoid arthritis,
10 including my family and me, every day is a
11 challenge. But it is so very exciting and
12 invigorating to have survived RA and know that for
13 the first time in 31 years viable treatment options
14 are available that really do reduce the pain,
15 suffering and disability, and can potentially curb
16 the disease's destructive course.

17 In conclusion, it is my personal
18 experience that Enbrel is safe and effective. In
19 short, it works and works magnificently, like
20 nothing else before it. Through my work with the
21 Arthritis Foundation I have met many, many other
22 Enbrel users. Their comments to me have been the
23 same, Enbrel is safe and effective. In fact, the
24 expression one hears frequently regarding Enbrel is
25 that "it has given me my life back" and so it has.

1 Thank you.

2 DR. WILLIAMS: Thank you for your
3 comments. I will remind the last two speakers that
4 public comments should be limited to five minutes.
5 The next one is Elizabeth Bachorik.

6 MS. BACHORIK: Good morning, Mr. Chairman
7 and members of the panel. My name is Elizabeth
8 Bachorik. I am from Centerville, Virginia. I have
9 suffered from Crohn's disease for 12 years. My
10 most recent flare up with it has brought me
11 literally to my knees, at least it did before
12 Remicade. I also want to just point out I am not a
13 paid spokesperson here today.

14 It all started after the birth of my son,
15 which is probably in about 1997. Crohn's was
16 acting pretty quiescent at the time and the only
17 therapy was corticosteroids and immunosuppressive
18 drugs, and it was keeping things quiescent for a
19 long time. But then development started happening
20 due to the disease. I started to get pyoderma
21 lesions all over my legs, making me debilitated in
22 walking at times. It got to a point where I had to
23 go in for surgery for a right colectomy. They
24 found that my right colon was completely strictured
25 and narrowed and disease had manifested completely.

1 We were hoping that after the right colectomy I
2 would be free from Crohn's for quite a while and I
3 would be able to lead at least a semi-normal life
4 for a little bit.'

5 Little did we know that a month later an
6 abscess would erupt out through the abdominal wall
7 causing a great deal of pain and being
8 incapacitated for a little bit. After that, a
9 fistula erupted about a week later, causing me to
10 go on IV therapy for nutrition and basically unable
11 to eat for a long time, for many months, with only
12 the ingestion of water. Being a new mother, this
13 was very debilitating as I was only able to
14 basically put up with a TPN all day and get through
15 the day.

16 It became clear that if there wasn't a
17 drug administered systemically that this disease
18 was going to get ahead of us, and it was ravaging
19 very quickly. Another surgery came about, and
20 after that surgery another fistula erupted. This
21 was an ongoing pattern that was happening and my
22 life was becoming diminished. I can honestly say
23 here, in front of you today, I would never have
24 believed two years ago I would be standing here.
25 Remicade has reversed all those incidences that I

1 was enduring completely. I am no longer on TPN
2 therapy. I have been eating solid food ever since
3 we started Remicade. I have no more pyoderma
4 lesions. I had a temporary ileostomy to help heal
5 these fistulae. The ileostomy became out of
6 control. I was having many problems with that. It
7 was becoming very unmanageable and I was back on
8 TPN with an ileostomy.

9 So, as you can see, all the surgeries and
10 all the corticosteroids and the traditional drugs
11 were not working, and Remicade changed all that. I
12 am now eating solid foods. I am leading a very
13 productive life. I went from merely existing to
14 now working part time, going back to school. I am
15 actually going back to school for nursing, and my
16 life has changed drastically. I can't tell you how
17 grateful I am to have a drug like Remicade to
18 change my life. It has not only changed it but it
19 has literally saved it. I was on long-term
20 morphine for pain for many, many months and I am
21 now pain free. I can honestly stand before you and
22 say I am fistula free. I realize that by taking
23 Remicade, not only does it heal fistulae, active
24 fistulae, it prevents them because ever since the
25 initial dose of Remicade I have not had any. So, I

1 just want to say thank you again and keep up the
2 good work.

3 DR. WILLIAMS: Thank you. I apologize for
4 mispronouncing your last name. Our final comment
5 will be by Carl Lowe.

6 MR. LOWE: Good morning, Mr. Chairman,
7 members of the committee. I am happy that you have
8 given me the opportunity to come this morning. I
9 am not a paid representative of Centocor, by the
10 way. I am on my own.

11 I want to tell you a little bit about the
12 onset and the treatment and the condition of my
13 disease now. I am a rheumatoid arthritis sufferer,
14 and the RA that hit me hit with a vengeance very
15 quickly. In June of 1999 -- I live in the country,
16 in Roanoke County and I have quite a bit of uphill
17 and downhill land. We were clearing some and we
18 worked pretty hard for a couple of days, and I went
19 to bed one night and had a lot of body aches, and I
20 was thinking tomorrow morning I would be fine. The
21 next morning I couldn't get out of bed. I thought,
22 "boy, I'll tell you, I've really worked hard but I
23 didn't work that hard."

24 After about a day or two of this when it
25 didn't get any better, I went to see my local

1 family practitioner. He did some examination and
2 he said, "maybe I'd better refer you to somebody
3 else. I don't know what's going on." So, he
4 referred me to the local rheumatologist that I go
5 to now, Dr. Limmer. I was diagnosed with RA and
6 Dr. Limmer said, "I can take care of your symptoms
7 but I can't cure your disease." So, he put me on
8 methotrexate, Relafen and hydrocodone, with a 5 mg
9 per day dose of prednisone. I was on that and the
10 symptoms were somewhat eased but not fully. I
11 still had a lot of pain, had to use a cane to get
12 around and my physical activity outside my house
13 was extremely limited.

14 After a while, I went into the examination
15 room one morning and he said, "I've got somebody I
16 want you to talk to but, first, let me tell you
17 about something I want you to try. It's called
18 Remicade." And, he told me about Remicade. He
19 told me about the price and the whole thing, and he
20 was very open to me. He said, "I want you to talk
21 to the detail man from the company; he'll give you
22 a video and some brochures. You read that and come
23 back and we'll give you a dose."

24 Well, about three or four days later I
25 came in for my first infusion. The infusion takes

1 about three and a half hours. You sit quietly and
2 it has given me a lot of opportunity to read, and
3 so forth, and I don't really mind needles that
4 much. Three days after the first infusion I began
5 to feel some relief of the symptoms. I received
6 another infusion in two weeks. Shortly after the
7 two-week infusion the symptoms were very much
8 eased. I could get around; I could walk; I could
9 raise my hands above my shoulders; I could go
10 outside and walk around on the hills and the area
11 around my house.

12 After about another infusion, the pain was
13 totally gone. I don't take any pain medication any
14 more. I still take the methotrexate and Relafen
15 but I lead a normal life. As I said in a recent TV
16 interview at our local station, I have been given
17 my life back. Remicade is, as far as I am
18 concerned, a miracle drug. I am sure there are
19 some things about the drug that are unknown at the
20 present time, and that really doesn't affect me at
21 the present time. I have experienced no harmful
22 side effects. I buy and sell used books and at
23 times I have to lift quite a large box of books --
24 I go to a person's house and buy a library. I cut
25 my own grass, and I have a walk-around push mower

1 and I cut an acre and a half of lawn, and it is all
2 uphill and downhill. I was telling one of the
3 gentlemen this morning that I only have about 15
4 square feet of level land on my property. I live
5 in the mountains and I wouldn't live anywhere else,
6 but it is hard to cut the grass, but I can cut the
7 grass. I can do what I need to do. I have a large
8 home and we heat with gas, but I am sort of a
9 peculiar person, I like to burn wood. I cut my own
10 wood. I split my own wood and I do it all without
11 any additional pain medication or anything. That
12 is due to Remicade. I live a normal life.

13 I am very happy that this medicine was
14 developed and I applaud the researchers who did so,
15 and I appreciate your efforts in following the
16 trials and the use of this medication to ensure
17 that users, such as myself, will know everything
18 about it and will be able to look for those things
19 that might cause some problems in the future.
20 Thank you very much for your time, and I appreciate
21 it.

22 DR. WILLIAMS: And thank you for coming.
23 We would like to thank all four of the patients for
24 taking the time to come and give their comments to
25 us. We will now move on to hear from the two

1 sponsors, and the first we will hear from is from
2 Immunex and we will turn the time over to Dr.
3 Daniel Burge.

4 **Immunex Presentation**

5 **Etancercept Post-Marketing Surveillance**

6 DR. BURGE: Good morning, members of the
7 committee, the FDA, ladies and gentlemen.

8 [Slide]

9 It is a pleasure to be here today to
10 provide a review of the safety of etancercept
11 which, as you are all aware, has become well
12 established as a significant new therapy for
13 patients with rheumatoid arthritis. We have been
14 asked by the FDA to focus our attention today on
15 communication with physicians and patients on the
16 efforts on which we are engaged to evaluate further
17 the safety of etancercept.

18 [Slide]

19 Our presentation will begin with a brief
20 discussion of the etancercept post-marketing
21 surveillance system that has generated the data
22 that you have reviewed in the briefing documents.
23 This will provide insight into some of the unique
24 elements of the etancercept post-marketing
25 surveillance system.

1 Dr. William Wallis will then discuss the
2 evaluation of the safety data, including
3 corresponding epidemiology, and will discuss our
4 communications to healthcare providers and
5 patients. I will conclude by describing for you
6 the multiple studies that are in place to deepen
7 our understanding of adverse events reported in the
8 etancercept clinical experience. These studies, in
9 conjunction with the post-marketing surveillance
10 system, constitute our pharmacovigilance program.

11 [Slide]

12 We have a group of consultants with us
13 here today, Dr. Bates, from the Arkansas Department
14 of Health; Dr. Brodsky, a hematologist from Johns
15 Hopkins; Dr. Caligiuri, an oncologist from Ohio
16 State University; Dr. Eley, an
17 oncologist/epidemiologist from Emory University;
18 Dr. Johnson, an epidemiologist from the University
19 of Washington; Dr. Lublin, a neurologist from Mt.
20 Sinai Hospital; and Dr. Paulus, a rheumatologist
21 from UCLA.

22 [Slide]

23 In overview, rheumatoid arthritis clinical
24 trials have demonstrated a favorable safety profile
25 for etancercept. We have developed a number of

1 programs that have enhanced post-marketing
2 reporting by physicians and patients and create a
3 clear picture of the etancercept experience. The
4 benefit to risk of etancercept remains strongly
5 positive. We are committed to collection and
6 assessment of safety data and communication to the
7 community.

8 [Slide]

9 As you well know, etancercept is the
10 dimeric TNF receptor fusion protein that is made up
11 of fully human TNF receptor and a portion of fully
12 human IgG. The TNF receptor is able to bind TNF
13 and lymphotoxin-alpha with high affinity. These
14 cytokines are, thus, made biologically unavailable
15 for interaction with cell-bound receptors. The
16 human protein has low immunogenicity and is not
17 capable of activating complement or initiating
18 complement-mediated cell lysis. The dosing
19 schedule of etancercept maintains stable serum
20 levels throughout the treatment period.

21 [Slide]

22 Enbrel was initially approved for
23 commercialization in November of 1998 for the
24 reduction of signs and symptoms of rheumatoid
25 arthritis, and was approved as either monotherapy

1 or in combination with methotrexate.

2 [Slide]

3 In May of 1999 Enbrel was additionally
4 approved for the treatment of juvenile rheumatoid
5 arthritis.

6 [Slide]

7 In June of 2000 Enbrel was demonstrated to
8 inhibit radiographic progression, and was approved
9 for early rheumatoid arthritis patients as an
10 initial disease modifying agent.

11 [Slide]

12 The experience with etancercept continues
13 to expand, with over 2000 rheumatoid arthritis
14 patients, over 600 outside of North America having
15 received etancercept in clinical trials for over
16 4300 patient years, and over 100,000 patients have
17 received commercial etancercept, over 9000 outside
18 of North America for over 116,000 patient years.

19 [Slide]

20 The average patient in rheumatoid
21 arthritis clinical trials is 50 years old and has
22 had rheumatoid arthritis for about 7 years. About
23 half received concomitant corticosteroids, and 14
24 percent have received concomitant methotrexate.
25 Patients receiving commercial etancercept appear

1 similar to those in the clinical trials, except
2 that they have had rheumatoid arthritis for a
3 longer period of time and a higher percentage are
4 also receiving methotrexate.

5 [Slide]

6 In clinical trials the only event that
7 occurred with increased frequency in etancercept
8 treated patients was injection site reactions.
9 Other adverse events occurred in similar
10 proportions in placebo and etancercept groups.
11 Additionally, in follow-up in long-term studies,
12 which include patients who have received
13 etancercept for more than 5 years, no new concerns
14 have been revealed. However, these clinical trials
15 are not sized for rare events and although the
16 patients receiving commercial etancercept appear
17 similar to trial patients, some observers have
18 expressed that trials may not accurately represent
19 clinical practice experience.

20 [Slide]

21 Post-marketing surveillance and
22 post-marketing reports are a well established
23 mechanism for capturing safety information from
24 real-world clinical practice. There are precedents
25 with other products that facilitated reporting

1 systems result in higher than typically observed
2 volumes of adverse event reports. This results in
3 earlier collection of clinical practice experience.

4 [Slide]

5 We have developed multiple programs that
6 have created a facilitated reporting system unique
7 among DMARD therapies. These programs, though not
8 initiated for the purpose of adverse event
9 reporting, have greatly enhanced reporting by
10 consumers. Since commercial launch of etancercept,
11 a toll-free help line, 1-888-4-ENBREL, has been
12 available and is prominently displayed on every
13 carton of etancercept.

14 [Slide]

15 The ENLIVEN program provides etancercept
16 patients educational materials on a routine basis;
17 provides safety information and provides the
18 toll-free hotline number. Over 40,000 etancercept
19 patients have enrolled in the ENLIVEN program.

20 [Slide]

21 The enrollment program was set up to
22 manage the strong demand for etancercept. In order
23 to ensure access to therapy, every etancercept
24 patient participates in the enrollment program and
25 contacts the company through the same toll-free

1 line.

2 [Slide]

3 Consumer reports of adverse events often
4 lead to follow-up calls to healthcare providers.
5 These follow-up calls further enhance adverse event
6 reporting. All these programs have contributed to
7 considerable ongoing interaction with patients
8 receiving etancercept therapy.

9 [Slide]

10 Over 480,000 phone contacts, an average of
11 more than four contacts for every patient who has
12 ever received etancercept, have facilitated over
13 20,000 adverse event reports. Although the vast
14 majority of these reports are considered medically
15 non-serious, reporting of serious events has been
16 proportional to the number of phone contacts.
17 Efforts are made to follow up all serious adverse
18 events with a healthcare provider.

19 [Slide]

20 This graph, constructed from information
21 available from the FDA adverse event reporting
22 system via Freedom of Information, shows the number
23 of healthcare provider reports regarding each of
24 the three rheumatoid arthritis products approved in
25 1998. The volume of consumer reports with

1 etancercept stimulates healthcare provider reports
2 as the follow-up phone contacts confirm or clarify
3 information from patients.

4 Importantly, for etancercept almost half
5 of the serious reports from healthcare providers
6 have been initiated in this manner by consumers,
7 most of which would not be captured in the
8 traditional passive spontaneous reporting system.
9 This additional information allows us to provide
10 better support for physicians and patients.

11 [Slide]

12 Facilitated reporting of etancercept
13 results in improved capture of adverse events
14 including serious events. This more complete data
15 set allows more prompt recognition of potential
16 signals. More in depth analysis of these events
17 can then be initiated using case review, study of
18 epidemiology and, if appropriate, additional
19 studies may be started that target these events.

20 [Slide]

21 Dr. Wayne Wallis will now discuss analysis
22 of safety data, along with the corresponding
23 epidemiology and the communications to physicians
24 and patients regarding the safety data.

25 **Safety Data, Epidemiology and Communications**

1 DR. WALLIS: Thank you, Dan.

2 [Slide]

3 I will review some of the specific safety
4 data that has already been presented in part by Dr.
5 Siegel and Dr. Braun from a different vantage
6 point. First, I would like to take just a few
7 moments to revisit some of the challenges of
8 working with post-marketing adverse event reports
9 both at the case level and at the population level.

10 We all agree that reporting rates, because
11 of under-reporting, are not comparable to true
12 incidence, but we all invoke benchmark incidence
13 figures for perspective in evaluating adverse event
14 reporting rates. Finally, I would like to
15 emphasize that the reports for all of the safety
16 observations we will review are infrequent in the
17 RA population receiving etancercept therapy, and
18 have been promptly communicated in the product
19 label.

20 [Slide]

21 I will briefly review some of the specific
22 safety observations as outlined on this slide,
23 chosen for this discussion as they were included in
24 the FDA briefing document.

25 [Slide]

1 One of the challenges of post-marketing
2 case reports, as you know, is frequently incomplete
3 data, unverified diagnoses and duplicate reports.
4 Because TNF antagonism is a new and fundamentally
5 different type of therapy, Immunex made a
6 substantial commitment up front at the time of
7 approval to have serious adverse event reports
8 extensively characterized, and to assure highest
9 possible quality of reporting. We believe that the
10 care with which we characterize reports supports
11 deeper understanding of the product safety profile.

12 [Slide]

13 Another challenge in post-marketing safety
14 work is in understanding the expected background
15 incidence of events, not only in the general
16 population but also in the RA population, and
17 ideally in an RA population that matches well with
18 the group receiving etanercept therapy, typically
19 with long-standing RA, approximately half on
20 concurrent corticosteroids and a substantial
21 fraction receiving methotrexate therapy as well.
22 We think it is important to understand the impact
23 of disease severity, comorbidities and concomitant
24 medications in considering whether the number of
25 observed events exceeds the number expected.

1 [Slide]

2 Acknowledging these limitations, we can
3 review some specific observations. The
4 epidemiology of cancer in RA patients reveals that
5 most malignancies occur with the same incidence and
6 prevalence as in the general population. The major
7 exception is lymphoma where the incidence in RA
8 patients is 2- to 3-fold higher than the general
9 population. One study, from Baecklund Kleriscog,
10 from the Swedish national RA registry, indicates
11 that lymphoma risk is increased up to 26-fold in RA
12 patients with higher inflammatory disease activity.

13 [Slide]

14 The initial etancercept product label,
15 which was outlined by Dr. Siegel and which is in
16 the briefing document, indicated that malignancies
17 had been observed in clinical trials and that the
18 long-term effect of etancercept therapy on
19 malignancy is unknown. Because of this, we
20 carefully monitor rates and types of malignancies
21 as a core commitment for the etancercept
22 pharmacovigilance program. The 38 malignancies
23 observed in the etancercept RA trials is similar to
24 the 39 expected using the National Cancer
25 Institute's SEER database. RA patients have been

1 followed for more than 5 years in clinical trials
2 and there has been no increase in the rate of
3 malignancies over time. The number of malignancies
4 from post-marketing reports is well below the
5 expected incidence and the types of malignancies
6 are characteristic of those typically seen in RA
7 patients.

8 [Slide]

9 Five cases of lymphoma have been observed
10 in etancercept RA trials. This number is similar
11 to the number expected in the RA population with
12 moderate disease severity. Post-marketing reports
13 have occurred at the rate of approximately 0.3/1000
14 patient years, which is the expected number for the
15 general population but lower than the incidence for
16 the RA population. There has been no cumulative
17 increase in reporting rate over time, and the
18 proportion of histologic subtypes is consistent
19 with what has been described in RA patients
20 previously. We continue to carefully monitor both
21 rates and types of malignancies, again, as part of
22 our ongoing pharmacovigilance program.

23 [Slide]

24 In preparing for this forum we thought
25 that a brief review of the history of demyelination

1 events, in addition to the history described by Dr.
2 Siegel, would be helpful for those who are
3 considering this subject for the first time.

4 Very briefly, we became aware of very rare
5 reports of patients with conditions associated with
6 demyelination, but the number of these events did
7 not seem to be above a background rate one might
8 anticipate in post-marketing reports. It was these
9 initial cases, in conjunction with the literature
10 that Dr. Siegel described, that led us to implement
11 the product label change. Both of those studies,
12 one with infliximab and one with etancercept, were
13 associated with worsening of multiple sclerosis.

14 [Slide]

15 In June of 2000 we initiated an addition
16 to the etancercept product label advising
17 clinicians to exercise caution in patients with a
18 history of demyelinating disorders, and this was
19 later followed by a letter to healthcare
20 professionals.

21 Here is the language regarding
22 demyelination in the product label, which you can
23 review in detail in the briefing documents. The
24 product label emphasizes that the observed events
25 are a spectrum of disorders, and encourages caution

1 in patients with prior demyelinating conditions.

2 [Slide]

3 This slide contrasts the expected
4 incidence and prevalence of MS cases, Ms relapses
5 and optic neuritis cases with the numbers of
6 reports observed. The reported numbers of events
7 reflect adjudication this past March by an
8 Immunex-convened advisory panel of neurologists
9 with expertise in demyelinating conditions. The
10 expected numbers reflect background epidemiology
11 for the general population, with no adjustment for
12 gender or RA, possibly relevant as both RA and MS
13 are predominantly female conditions. There was 1
14 definite case of MS with 4 probable and up to 7
15 expected, and 8 MS relapses. Since most patients
16 with MS have the relapsing-remitting form of MS, we
17 would expect approximately 83 relapses among
18 patients receiving etanercept therapy. There were
19 3 cases with optic neuritis, with 5 expected; 7
20 cases fit into other categories for which the
21 background epidemiology is not well established,
22 some of which were described by Dr. Siegel. There
23 is no literature on the epidemiology of
24 demyelinating conditions in patients with
25 rheumatoid arthritis.

1 [Slide]

2 The expert panel that adjudicated the
3 diverse and heterogeneous case reports was
4 comprised of rheumatologists, neurologists and
5 others. Our intent was to classify cases into
6 categories permitting evaluation beyond individual
7 case attribution analysis. One of the challenges
8 in this work is the issue of case definition. We
9 included any case for review when a physician or
10 patient invoked the term demyelination or where
11 patients had any of the known demyelinating
12 conditions. Review included detailed analysis of
13 all case materials, including MRI scans when
14 available. The panel concluded that the causal
15 relationship between etancercept and demyelination
16 events was uncertain; that the product label
17 conveys the appropriate information for informed
18 prescribing; and recommended further careful safety
19 surveillance.

20 [Slide]

21 The term "seizures" was also added to the
22 product label in August, 2000 and is discussed in
23 the briefing document. The clinical patterns in
24 these reports are highly varied, many of which are
25 reasonably explained by comorbidities and it is

1 difficult to assign a causal role for etancercept
2 in these cases with certainty.

3 [Slide]

4 Individual reports of patients with
5 pancytopenia, including aplastic anemia, are
6 described, again, in the FDA briefing document. In
7 December, 2000 we convened a panel of hematologists
8 and epidemiologists with expertise in bone marrow
9 dyskrasias to review all reports of pancytopenia.
10 They concluded that there were 3 cases that met the
11 clinical diagnostic criteria for aplastic anemia,
12 and we have become aware of one additional case
13 since that time. This panel also recommended
14 further careful safety surveillance.

15 [Slide]

16 The international agranulocytosis and
17 aplastic anemia study, widely recognized as the
18 most rigorous benchmark study for incidence of
19 aplastic anemia, found that the risk of aplasia in
20 RA patients is increased from 2.6- to 23-fold.
21 Based on these findings, the expected number of
22 cases in the 120,000 patient years of etancercept
23 experience ranges between 0.6 to 5.7.

24 [Slide]

25 Pancytopenia and aplastic anemia were

1 added to the product label in August, 2000, and
2 later amended in conjunction with a letter to
3 healthcare professionals. The label recommends
4 caution in patients with preexisting hematologic
5 disorders, and both the product label and the
6 patient package insert suggest that patients seek
7 attention if they develop symptoms suggesting
8 pancytopenia.

9 [Slide]

10 We have also received rare reports of
11 patients with intestinal perforation. Most of
12 these adverse events were related to diverticula
13 and 2 occurred in the setting of colonoscopy for
14 other conditions. This condition was added to the
15 product label this past January. It is widely
16 accepted that corticosteroids predispose patients
17 to colonic perforation, and 81 percent of the
18 patients in these reports were receiving concurrent
19 corticosteroid therapy.

20 [Slide]

21 There are rare reports of RA patients with
22 rashes considered analogous to discoid or subacute
23 cutaneous lupus. Those reports were added to the
24 product label in August, 2000 and then amended in
25 January of this year. Some cases have a

1 corresponding skin biopsy, most with a positive
2 antinuclear antibody, and rarely patients have
3 additional positive serologies. None have had
4 pleurisy or other features suggestive of systemic
5 lupus.

6 [Slide]

7 Although there were studies even in the
8 pre-corticosteroids era suggesting a higher rate of
9 infections in RA patients, the precise incidence of
10 serious infections in RA was previously not well
11 established. Reports of serious infections shortly
12 after etancercept approval, again described by Dr.
13 Siegel, led to product labeling changes and a
14 letter to healthcare professionals that, again, are
15 enclosed in the briefing document for review.
16 Since that time, 2 studies described the incidence
17 of such infections in RA patients, ranging from
18 0.03 to 0.09 events per patient year. The
19 incidence observed in etancercept RA trials falls
20 within that range, 0.04 events per patient year.
21 The etancercept post-marketing rate for serious
22 infections is lower.

23 [Slide]

24 Drs. Doran and Gabriel, with the Rochester
25 Epidemiology Group, and Dr. Singh and colleagues,

1 with Aramis, have shown that serious infections are
2 with patient's degree of disability, comorbidities
3 such as lung and heart disease and most strongly
4 with concurrent corticosteroid therapy. These
5 findings emphasize the importance of considering
6 confounding elements such as disease severity,
7 comorbidities and concurrent medications, as
8 outlined by Dr. Braun, in evaluating both the case
9 reports and adverse event reporting rates.

10 [Slide]

11 Opportunistic infections are known to
12 rarely arise in RA patients, especially in the
13 setting of anti-metabolite therapies or high dose
14 corticosteroids. But, in etancercept
15 post-marketing reports these cases have been rare.
16 This slide outlines the numbers of clinically
17 significant opportunistic infections. A large
18 proportion of patients were receiving concurrent
19 corticosteroids and/or methotrexate, leflunomide,
20 azathioprine or cyclophosphamide.

21 [Slide]

22 Tuberculosis has recently received a great
23 deal of attention and can also be considered a type
24 of opportunistic infection. We know that the
25 background incidence in the general population, if

1 one age and sex adjusts for the distribution of
2 etancercept-treated patients, is 8.2/100,000
3 patient years. An important risk factor for TB is
4 corticosteroid therapy. As you recall,
5 approximately half of patients receiving
6 etancercept were also receiving corticosteroids,
7 and we assume that the relative risk for TB in such
8 patients would, therefore, be higher than in the
9 general population. There are no published reports
10 that define the true incidence or prevalence of TB
11 in RA patients.

12 [Slide]

13 Extrapolating from the incidence in the
14 general population, we would have expected 10 cases
15 and we have received 11 reports of patients
16 diagnosed with tuberculosis, none from etancercept
17 RA trials. Eight had localized infections. Of the
18 localized infections, 5 are pulmonary and 3 are
19 extrapulmonary. As for risk factors, 2 had
20 diabetes and 7 were receiving corticosteroids
21 and/or methotrexate. Seven patients were diagnosed
22 by culture, 1 by biopsy, and 2 cases were both
23 culture negative and smear negative.

24 [Slide]

25 We have had further insights from 29

1 patients with a pre-etancercept history of clinical
2 TB. Again, part of this was described by Dr.
3 Siegel. From RA trials in both the United States
4 and in Europe where TB screening has not been
5 performed, and from post-marketing reports where
6 follow-up has been obtained in all cases, no
7 reactivation has been observed and in the trial
8 patients the average duration of etancercept
9 therapy is now over 540 days. We have also had 14
10 patients with a known positive tuberculin skin test
11 without prior clinical TB, 7 from etancercept RA
12 trials and 7 from post-marketing reports, none of
13 whom have developed TB reactivation.

14 [Slide]

15 The CDC guidelines recommend targeted and
16 not global screening in groups that are at high
17 risk for TB, including recent immigrants from
18 high-prevalence countries, patients receiving
19 higher dose corticosteroids, and patients with
20 underlying diseases that are associated with
21 immunosuppression. Immunex fully supports these
22 guidelines.

23 [Slide]

24 The product label was updated in January
25 of this year to include language regarding the

1 potential role for concomitant immunosuppressive
2 therapies predisposing to infections and the rare
3 cases of tuberculosis. We continue to carefully
4 monitor for potential additional reports.

5 [Slide]

6 Etancercept has led the way in a
7 fundamental new class of therapies for
8 rheumatologists treating patients with RA. The
9 Immunex facilitated reporting system has helped all
10 of us expeditiously learn a great deal about the
11 etancercept safety profile. Serious adverse events
12 are infrequent and a causal relationship for all of
13 these events is difficult to establish with
14 certainty. We have actively communicated our
15 findings in the product label and through
16 publications and presentations, ACR hotlines,
17 revisions in the patient package insert and in the
18 Enliven patient education program. Our commitment
19 is to continue to provide timely information that
20 supports wise and informed decision-making by both
21 patients and the medical community. Thank you.

22 **Pharmacoviligance Program -- Objectives**

23 [Slide]

24 DR. BURGE: At the time of
25 commercialization, Immunex had a substantial