

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE MEETING

NUMBER FORTY-FIVE

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OPEN SESSION

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Thursday, April 17, 1997

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The Advisory Committee met in the Grand Ballroom at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, at 8:30 a.m., Joseph McGuire, Jr., M.D., Chairman, presiding.

PRESENT:

JOSEPH McGUIRE, JR., M.D., Chairman
TRACY RILEY, Executive Secretary
DENISE BUNTIN, M.D., Member
S. JAMES KILPATRICK, JR., Ph.D., Member
JOEL MINDEL, M.D., Member
MILTON ORKIN, M.C., Member
SUSAN COHEN, B.S., Consumer Representative
E. DENNIS BASHAW, Pharm.D., FDA
VINCENT GUINEE, M.D., FDA
KATHRYN O'CONNELL, M.D., FDA
LISA RARICK, M.D., FDA
DEBORAH SMITH, M.D., FDA
JONATHON WILKIN, M.D., FDA
LOUIS R. CANTILENA, M.D., Ph.D., Consultant
JOHN J. DiGIOVANNA, M.D., Consultant
EDWARD LAMMER, M.D., Consultant
ROBERT ARMSTRONG, M.D., Industry Speaker
LYNN McKINLEY-GRANT, M.D., Participant

ALSO PRESENT:

HILAL MARADIT, M.D.
TARA ROLSTAD

A-G-E-N-D-A

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

2 8:44 a.m.

3 CHAIRMAN McGUIRE: Good morning. My name
4 is Joe McGuire, and I'll be chairing the 45th Meeting
5 of the Dermatologic and Ophthalmic Drug Advisory
6 Committee.

7 I'd like to welcome the representatives
8 from Roche, the sponsor, and representatives of the
9 Agency.

10 What I'd like to do, before we begin our
11 work, is to start around the table with Doctor Wilkin,
12 and have everyone identify himself, herself.

13 DOCTOR WILKIN: I'm Jonathon Wilkin,
14 Director of the Division of Dermatologic and Dental
15 Drug Products, FDA.

16 DOCTOR O'CONNELL: I'm Kathryn O'Connell,
17 Medical Reviewer, Division of Dermatologic and Dental
18 Drug Products, FDA.

19 MR. BASHAW: I'm Dennis Bashaw, I'm the
20 Pharmacokinetics Team Leader from the Division of
21 Pharmaceutical Evaluation III.

22 DOCTOR KILPATRICK: I'm Jim Kilpatrick,
23 Professor of Biostatistics at the Medical College of
24 Virginia, Virginia Commonwealth University.

25 DOCTOR MINDEL: Joel Mindel, the

1 Departments of Ophthalmology and Pharmacology, Mount
2 Sinai Medical Center, New York.

3 DOCTOR ORKIN: Milt Orkin, private practice
4 and Clinical Professor of Dermatology, University of
5 Minnesota/Minneapolis.

6 EXECUTIVE SECRETARY RILEY: Tracy Riley,
7 I'm the Executive Secretary of the Dermatologic and
8 Ophthalmic Drugs Advisory Committee.

9 DOCTOR BUNTIN: I'm Denise Buntin. I'm a
10 Dermatologist in private practice in Nashville,
11 Tennessee, and Adjunct Associate Professor at
12 Vanderbilt.

13 DOCTOR DiGIOVANNA: John DiGiovanna, I'm a
14 Dermatologist. I'm an Adjunct Investigator at the
15 NIH, and am in the process of moving to the Division
16 of Dermatopharmacology at Brown University.

17 MS. COHEN: I'm Susan Cohen, and I'm a
18 consumer member.

19 DOCTOR MCKINLEY-GRANT: I'm Lynn McKinley-
20 Grant, I'm a Dermatologist, Assistant Clinical
21 Professor at George Washington University and
22 Washington Hospital Center, and I'm a member of the
23 Non-Prescription Drug Advisory Committee.

24 DOCTOR RARICK: I'm Lisa Rarick, I'm an
25 Obstetrician, Gynecologist and the Director of the

1 Division of Reproductive and Urologic Drug Products at
2 the Food and Drug Administration.

3 CHAIRMAN McGUIRE: Well, thank you. There
4 weren't many surprises there.

5 It's about 5:30 my time, and so if things
6 drag just be stimulating, but I'll be better this
7 afternoon.

8 Is Doctor Lammer here? We actually have a
9 chair for you up here.

10 At this point, Tracy Riley, who is the
11 Executive Secretary, will ask us about Conflict of
12 Interest and give us some general rules.

13 EXECUTIVE SECRETARY RILEY: Good morning.

14 The following announcement addresses the
15 issue of conflict of interest with regard to this
16 meeting, and is made a part of the record to preclude
17 even the appearance of such at this meeting.

18 Based on the submitted agenda and
19 information provided by the participants, the Agency
20 has determined that all reported interests and firms
21 regulated by the Center for Drug Evaluation and
22 Research present no potential for a conflict of
23 interest at this meeting.

24 In addition, we would like to disclose for
25 the record that Doctor Lynn McKinley-Grant and her

1 employer, Washington Hospital Center Dermatology
2 Associates, previously studied Soriatane, the drug
3 coming before the committee for consideration.

4 The Advisory Committee is looking at the
5 management of teratogenic risks associated with
6 Soriatane in treating females of child-bearing
7 potential, while the Washington Hospital study was on
8 potential liver toxicity associated with the drug use.

9 Furthermore, Doctor McKinley-Grant has no
10 current involvement with respect to Hoffmann-La
11 Roche's Soriatane.

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

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

22 CHAIRMAN McGUIRE: We will now have an open
23 public hearing, and I think there's one representative
24 from the National Psoriasis Foundation.

25 Good morning.

1 MS. ROLSTAD: Good morning. It's also 5:30
2 my time, so I'm with you.

3 CHAIRMAN McGUIRE: I'll probably understand
4 everything you say then.

5 MS. ROLSTAD: Wonderful.

6 Good morning, I am Tara Rolstad, the Public
7 Information Director for the National Psoriasis
8 Foundation (NPF). The National Psoriasis Foundation
9 is a lay nonprofit organization committed to improving
10 the lives of people with psoriasis, through research,
11 advocacy and support of psoriasis research and
12 education. We are primarily supported by donations
13 from people with psoriasis. Approximately 20 percent
14 of our annual budget of \$2.5 million does come in the
15 form of various grants from pharmaceutical companies.
16 In the past 18 months, we have received \$4000.00 in
17 donations from Hoffmann-La Roche towards our operating
18 expenses and special programs. My testimony today,
19 and all related expenses, is completely funded by the
20 National Psoriasis Foundation.

21 The NPF represents 6.5 million Americans
22 with psoriasis, including over one million Americans
23 with moderate to severe cases of this disease. People
24 with severe psoriasis often contact the National
25 Psoriasis Foundation seeking information to assist

1 them in assessing the risks and benefits of various
2 therapies for psoriasis. They are generally an
3 informed, responsible group that is well aware that
4 their most effective therapy options are limited and
5 carry potentially significant risks.

6 These patients face a particularly
7 difficult situation. As we all know, there is no one
8 psoriasis therapy that will work for every patient.
9 Once a patient finds a therapy that does work for
10 them, they have to live with the knowledge that it may
11 stop working at any time. Even if the therapy
12 continues to help, the patient will need to rotate to
13 a different therapy after a certain time because all
14 therapies for severe psoriasis carry the risk of
15 potentially toxic side effects.

16 Medical advisors to the National Psoriasis
17 Foundation recommend that patients take advantage of
18 beneficial drug combinations and rotation of therapy
19 modalities so as to maximize benefit of useful
20 medications while minimizing the risk of serious side
21 effects. In practice, we are now finding lifetime
22 dose limits to the most useful therapies for severe
23 psoriasis, including PUVA and methotrexate.

24 Acitretin should be an important addition
25 to the list of available psoriasis therapies.

1 Retinoids can be quite effective in combination with
2 other psoriasis therapies such as PUVA, and such
3 combination therapy can actually reduce total dosage,
4 therefore reducing long-term risk of lifetime disease
5 from these side effects. Last week's PUVA study in
6 the New England Journal of Medicine only underlines
7 the importance of retinoids in combination therapy for
8 severe psoriasis.

9 For patients with pustular or erythrodermia
10 psoriasis, particularly women, their choices are
11 particularly limited, and these women are desperate
12 for effective treatment. As we testified in front of
13 a similar committee gathering in February of 1994, the
14 National Psoriasis Foundation believes that women with
15 severe psoriasis need access to this potentially
16 valuable psoriasis treatment. For some women, it may
17 be one only a few treatments that will work for them,
18 or possibly the only one. For women or young girls
19 with pustular or erythrodermia psoriasis, it may save
20 their lives. The fact that three years later the drug
21 is not yet FDA-approved means it is still unavailable
22 to these women.

23 It is clear to the National Psoriasis
24 Foundation that for some women the benefits of
25 potentially toxic psoriasis therapies outweigh the

1 risks. We have case histories in our files of women
2 who have voluntarily been sterilized so they could
3 gain access to etretinate. One woman told us, "Potent
4 drugs have given me my life, and allowed me to work.
5 I am on Tegison, and have chosen not to have
6 children." Theoretically, women would not need to
7 take such drastic steps if acitretin was available to
8 them.

9 These women are willing to actually forsake
10 having children in order to gain access to etretinate.
11 It is not unreasonable to believe that many, many of
12 these women would be responsible patients who would
13 readily comply with a post-treatment contraceptive
14 period to receive the potentially life-saving benefits
15 of acitretin while retaining the possibility of future
16 motherhood. These patients would be open and
17 receptive to any patient education programs that
18 communicated this message. We suggest that these
19 patients be properly informed and then allowed to
20 assume the risks and responsibilities of using these
21 types of medications.

22 The National Psoriasis Foundation does not
23 have the expertise to comment on the recommended
24 length of the post-treatment contraceptive period,
25 whether it should be the two years requested by the

1 manufacturer or some other time period. I am here
2 only to urge that a decision be made as quickly as
3 possible, and that the guideline for a post-treatment
4 contraceptive period be clear for both patient and
5 physician.

6 The National Psoriasis Foundation agrees
7 with the opinion that when defining the post-treatment
8 contraceptive period, a phrase such as "at least three
9 years" is unclear and confusing. In our experience
10 with women with severe psoriasis, it is extremely
11 likely that such phrasing could cause women to avoid
12 pregnancy or terminate pregnancy for long after three
13 years. Such phrasing, we think, would also make it
14 difficult for a physician to provide helpful guidance.

15 We feel that a firm, clear guideline would
16 prove most helpful to patients and physicians. Again,
17 let me emphasize, all available treatments for severe
18 psoriasis carry potentially toxic side effects,
19 ranging from liver or kidney damage to skin cancer.
20 It is absolutely vital that a young person looking
21 forward to decades, even 50 or 70 years, of necessary
22 psoriasis treatment, have access to all effective
23 treatment options as soon as possible. It is equally
24 vital that drug manufacturers and the FDA work
25 together to provide the patient with the clearest

1 information available, so that they and their
2 physician can make the most informed decision
3 possible. Only then can these people get on with
4 their careers, their personal relationships, and the
5 rest of their lives. We would ask that you work
6 toward that goal with all reasonable speed.

7 CHAIRMAN McGUIRE: Thank you very much.

8 Would anyone from the committee like to
9 direct questions? Yes.

10 DOCTOR KILPATRICK: Tara, I'm trying to get
11 a handle on the number of women who may be taking this
12 drug, if approved with suitable phrasing. You
13 mentioned, I think, please correct me, 1.5 million
14 currently in the United States with severe psoriasis,
15 but I am obviously interested in those who are women
16 of child-bearing age who may be taking it. Have you
17 any handle on the actual number?

18 MS. ROLSTAD: Well, actually, it's 1
19 million that we estimate to have moderate to severe
20 cases of the disease, and, unfortunately, we don't
21 have any knowledge or data that would define the
22 separation between moderate and severe disease. So,
23 we have to stick with that larger number, and to my
24 knowledge it's a fairly equal 50/50 split in the
25 gender, so at least a 1/2 million women would be

1 eligible for this treatment, although it would
2 probably be a much smaller number because some of
3 those women are moderate cases and can be controlled
4 with other therapies.

5 DOCTOR KILPATRICK: Perhaps the sponsor
6 could later address that issue.

7 One other question. You are asking us to
8 consider other phrasing than "at least three years,"
9 what type of phrasing are you thinking of would be
10 preferable to "at least three years"? I didn't get
11 the import of your message. What's wrong with "at
12 least three years"?

13 MS. ROLSTAD: Sure. "At least three years"
14 is not clear enough to give a woman, in my opinion,
15 and in our opinion, good guidance. As a woman of
16 child-bearing age, I know if I was facing that
17 situation, and a pregnancy occurred soon after that
18 or, perhaps, I wanted to become pregnant soon after
19 that, and soon after that, to a woman who is
20 considering, you know, the life and the health of her
21 child, could be a long time or a short time, it could
22 be months or it could be, if you want to be really
23 safe, it could be years, and then, perhaps, the woman
24 would be past time to have children.

25 So, if it's possible, and we would ask that

1 whatever the number the committee comes up and it
2 finally recommended, would be a formula that a woman
3 can feel comfortable with, and I know that's a very
4 difficult thing to ask, but that's the easiest thing
5 for the patient.

6 CHAIRMAN McGUIRE: I think Doctor
7 Kilpatrick's question is right on target, and we'll
8 hear that again, and again, and again.

9 The question is how much responsibility are
10 we placing on the mother or the woman, and how much
11 responsibility are we taking, and how can we define
12 the time, rather than leave it open ended. That's
13 what this meeting is about.

14 MS. ROLSTAD: Right, and I guess the point
15 of my comments were, these women are very aware that
16 pretty much any therapy they choose to control their
17 psoriasis may, at some point, cause them serious
18 health problems. There is nothing available without
19 those toxic side effects.

20 And so, the best they can ask for from you
21 is a clear guideline that they can evaluate all those
22 different risks.

23 CHAIRMAN McGUIRE: Doctor Mindel.

24 DOCTOR MINDEL: I'd like to say the same
25 question that's been raised, why hasn't your

1 organization given a firm, clear guideline in your
2 talk, and why is it you think we would be able to give
3 a firm, clear guideline?

4 MS. ROLSTAD: I'm sorry, I didn't catch the
5 first part, why haven't we given --

6 DOCTOR MINDEL: Why is it -- yes, why is it
7 you are not giving us a firm, clear guideline
8 representing the organization that you are, and why is
9 it you think we will be able to?

10 MS. ROLSTAD: It does seem unfair, doesn't
11 it, for me to ask that of you, but we are a lay
12 organization. We are an organization made up of
13 patient advocates, of people either with psoriasis or
14 people such as myself who have backgrounds in
15 completely non-health related fields. And, we look to
16 you for that because that's your expertise.

17 CHAIRMAN McGUIRE: Yes, Doctor DiGiovanna.

18 DOCTOR DiGIOVANNA: As an obviously
19 intelligent woman of child-bearing potential, and an
20 astute consumer, wouldn't you feel more informed if
21 you knew that after two or three, or whatever the firm
22 number of years, that there still was a small
23 declining risk, and wouldn't you feel deceived if you
24 were told that two years was a safe time, and then
25 after that two-year period there persists a small

1 risk?

2 MS. ROLSTAD: I think I understand your
3 question. If, say, the guideline given was two years,
4 and proof existed somewhere that there was risk after
5 that two-year period, and I was not informed of that,
6 of course I would feel deceived.

7 But, if the guideline was given that it's
8 two years, or three years, or whatever, and that's the
9 first, and after that there may or may not, or there
10 is, whatever it is, just to be clear to these women,
11 as clear as you can, where they may, indeed, forsake
12 the option completely, they may not even consider it,
13 or they may decide not to have children, which is
14 awfully harsh thing to have to decide as a woman.

15 CHAIRMAN McGUIRE: Are there other
16 questions from the committee?

17 Well, thank you. You certainly have
18 focused on what we're going to be troubled with for
19 the rest of the day.

20 MS. ROLSTAD: Thank you.

21 CHAIRMAN McGUIRE: Doctor Jonathon Wilkin
22 will make his introductory remarks.

23 DOCTOR WILKIN: Thank you, Mr. Chairman.

24 Already the topic, I think, has been laid
25 out, the essence of what the Agency would like to hear

1 feedback on from the committee.

2 As you know, we are very interested in the
3 final summary recommendations that the committee will
4 make to the Agency at the end of the day on this
5 issue, but you also note that we, at the FDA,
6 carefully consider and think about all of the comments
7 and insights that emerge during the deliberations
8 through the day. So, we are very much looking forward
9 to the discussions and deliberations on this
10 particular topic.

11 By way of background, if you look at the
12 briefing packages from the Agency, and from our
13 colleagues at Roche, you'll find an amazing
14 convergence of materials that are in the briefing
15 packages. I should point out that over the past six
16 months, that we have had very successful collaborative
17 interactions between the FDA team and our colleagues
18 at Roche on working on the label, and we have
19 addressed many of the issues that we had six months
20 ago, and we've finally gotten it down to one single
21 issue, where we believe that well-intentioned,
22 intelligent folks at Roche and the Agency are looking
23 at the same data, agreeing what these data are, but
24 they are erecting different edifices, if you will, on
25 top of this database.

1 And, it is a very difficult question,
2 that's why the committee is convening on this topic
3 today. We, again, will look forward to the questions
4 and comments that emerge, in addition to your final
5 comments at the end of the day.

6 The FDA team that works on Soriatane, all
7 the issues on Soriatane, is much larger than those of
8 us who are sitting at the table, and many of those
9 folks are in the FDA section here, but the members of
10 the team most closely related and directly involved
11 with this particular topic are Doctor Bashaw, Doctor
12 O'Connell and myself, and Doctor O'Connell will begin
13 our FDA presentation.

14 DOCTOR O'CONNELL: Good morning, everyone.
15 We want to thank you for your participation today. As
16 Doctor Wilkin pointed out, this is a very important
17 question, and we value your advice.

18 The schedule notes that I will speak and
19 then Doctor Bashaw will speak, and, actually, Doctor
20 Bashaw and I had decided to merge our talks for
21 clarity, because the issues are really interrelated,
22 so that members of the committee who have a packet,
23 actually, the slides are in order of me speaking,
24 Doctor Bashaw speaking, and then I'll come back. And
25 then at the end of all the presentations today, Doctor

1 Wilkin will make some comments about the thinking that
2 went behind our analysis of the data that Dennis and
3 I will present.

4 Could I have the first slide? As Doctor
5 Wilkin pointed out, the topic today is post-treatment
6 contraceptive advice, and, essentially, what I'm going
7 to refer to, and other speakers will refer to as the
8 post-treatment contraceptive period, is a phrase that
9 we can use while speaking, and what it refers to,
10 specifically, is the length of time that a woman
11 should avoid pregnancy after discontinuing Soriatane
12 treatment.

13 Before I go into the data that we are
14 considering, I want to reiterate what Doctor Wilkin
15 already said, that we are definitely on the same page
16 with the sponsor. We believe that Soriatane is a
17 valuable addition to dermatologic therapeutics. It's
18 efficacious in the treatment of a very serious
19 disease, and it poses less retinoid-associated
20 teratogenic risk than the drug that's currently on the
21 market, etretinate.

22 The issue today then isn't whether this
23 drug should be approved, the issue is how can we label
24 this drug in a most accurate way, given the
25 information that's now available.

1 Now, the goal of the Soriatane label, as we
2 see it, is the goal of any drug label, and that's to
3 guide and form management decisions to give physicians
4 and their patients the best information possible.
5 And, the ideal label for Soriatane, of course, would
6 provide a precise delineation of teratogenic risks, as
7 well as very directed procedures for avoiding that
8 risk.

9 But, to make a label like this, it would be
10 very helpful if we had definitive information about
11 the persistence of the teratogen in question in vivo,
12 the threshold concentration for the teratogenic risk,
13 and the scope of what are associated defects, in other
14 words, what are we looking for.

15 The problem is, as has been alluded to
16 already, is that when Soriatane was placed on the
17 European market, it originally had a recommendation
18 for two months avoidance of pregnancy based on the
19 half life, but it became evident in vivo in patients
20 that some people were forming etretinate who had never
21 taken etretinate. So, in other words, somehow the
22 acitretin was being converted back into etretinate.

23 Studies done by the sponsor have since
24 delineated the fact that ethanol participates in this
25 reaction, and so what we are faced with with this

1 information is how does this information affect the
2 teratogenic risk of Soriatane, and what post-treatment
3 contraceptive advice would be consistent with this
4 information.

5 So, for the purposes of our discussion this
6 morning, we basically have broken this problem down
7 into three questions for which we have information to
8 discuss. The first is what are the half lives of
9 acitretin and etretinate. The second is, what is the
10 threshold concentration for retinoid-associated
11 teratogenic risk, and then lastly, what do the
12 available data tell us.

13 And so, Doctor Bashaw is now going to
14 address the first question, and I will then come back
15 and address the other two. His question, basically,
16 since ethanol has been identified as a participant in
17 this process, the other issues that are pertinent to
18 his question is, does transesterification to
19 etretinate occur in the absence of ethanol ingestion?
20 And, secondly, is there a threshold concentration of
21 ethanol below which the reaction does not proceed?

22 Doctor Bashaw?

23 MR. BASHAW: Good morning. I'd like to
24 thank the committee for giving me the opportunity to
25 speak this morning.

1 What we are going to discuss in the next
2 few minutes is not the pharmacokinetics of either
3 acitretin or etretinate per se, what we are going to
4 be focusing on is the interaction between acitretin,
5 and alcohol, and speculate on the data we have, and
6 present what we know about the interaction right now.

7 What we are primarily focusing on, just as
8 a background, although I'm sure you all are well aware
9 of it, is the product, certainly, etretinate, is on
10 the market right now and is associated with a very
11 long half life, which is primarily due to its uptake
12 in fat stores in adipose tissue.

13 It, of course, is a pro drug, and what you
14 have is, you have out here an ester which is
15 hydrolyzed in the body and forms the active form
16 acitretin, which you see has a carboxylic acid out
17 here.

18 It has a much shorter half life. It has a
19 half life of approximately 60 hours, and is much more
20 amenable to being able to stop the drug and washing
21 out, in terms of eliminating total body stores very
22 quickly, in comparison to the parent drug, as you can
23 see it's the active metabolite, and it was developed
24 primarily to take advantage of that fact, that we had
25 a much shorter -- we had the active species, a much

1 shorter half life, it was developed primarily to take
2 advantage of these factors.

3 But, as Doctor O'Connell alluded to, in the
4 European studies it was found that patients who had
5 never been exposed to etretinate had actually -- had
6 only been exposed only to acitretin, had circulating
7 levels, and this was very concerning, because, again,
8 the whole focus was to make this shorter-active
9 metabolite, make this active species, and go ahead
10 with it.

11 The sponsor, to their credit, jumped on
12 this and did a number of in vitro and some in vivo
13 studies, and found that alcohol seemed to participate
14 in this reaction and drive it, so to speak, in
15 reverse, the metabolic reaction being etretinate to
16 acitretin, now it's going backwards.

17 So, studies were done, and the studies most
18 interesting to talk about is an in vivo study where
19 patients were given, in a crossover manner, a single
20 100 milligram dose of acitretin, either with or
21 without alcohol.

22 Now, what we have to note here is that
23 these subjects received a total of 101 mls of pure
24 alcohol which is administered over four hours as
25 basically some very strong screwdrivers.

1 What we should note about this study was
2 that after the crossover was done, it was found that
3 those patients who only received acitretin, no
4 alcohol, there were no circulating levels of
5 etretinate. However, when alcohol was administered in
6 these amounts, you had an area in the curve for
7 etretinate equivalent to approximately a five
8 milligram oral dose. So, there certainly is some
9 conversion, and it was proved definitively by the
10 study in humans.

11 The study certainly did delineate that this
12 was the reaction happening, but what the study did not
13 show is, it didn't show was there a threshold effect,
14 because, obviously, taking the drug and taking four
15 drinks, you know, hourly drinks, is a pretty much
16 unusual situation, and it didn't look at, you know, is
17 this a concentration-related effect, would lower
18 levels of alcohol have the same effect to the same
19 extent, is there some threshold concentration below
20 which this reaction does not take place? The study
21 did not show that.

22 Also, we have to give reflection to the
23 fact that this study was done, such that both the peak
24 levels of alcohol and the peak levels of acitretin
25 corresponded in about the same time frame. Again,

1 looking at this interaction, how many patients are
2 going to take acitretin and then go out on a binge,
3 certainly, some will, I mean, it happens, but it's an
4 unanswered question as to time spaciality here, if
5 levels of alcohol rise and fall, if we can then take
6 the drug later in the day, is there going to be
7 interaction, to what extent? The study left some
8 questions there.

9 And, another concern we have to have here
10 is that we know that alcohol dehydrogenase, the enzyme
11 primarily responsible for the inactivation and the
12 metabolism of alcohol in man, is variable among the
13 races. There is genetic defects in alcohol
14 dehydrogenase, and it's possible, though it's not
15 proven one way or the other, that people who are
16 deficient in alcohol dehydrogenase, who will then have
17 higher circulating levels of alcohol longer for any
18 given drink, might be at a higher propensity to form
19 more etretinate than normally would happen in most
20 subjects.

21 Certainly, we did show the interaction, but
22 the study did have some limitations. I think there is
23 some growth for further work in this area, especially
24 in terms of a dose response effect, giving -- measured
25 taking, say, a group of subjects and giving differing

1 amounts of alcohol along with the drug, to see, is
2 there some threshold effect, the concern being that,
3 is this reaction always going to take place? We know
4 that, certainly, many over-the-counter medications
5 contain alcohol, there's alcohol in some of the foods
6 we consume, is this is a process that's going to
7 happen always, or is there some threshold above which
8 it happens and below which it doesn't happen?

9 I think that that delineation of the
10 threshold effect, whether or not it exists, is a key
11 issue that needs to be looked at.

12 We are talking about half lives here. One
13 issue, we key in on the fact that we are really
14 talking about a very long time, we are talking with
15 etretinate, we are talking days. Usually, the
16 pharmacokineticists -- I did make one promise to my
17 colleagues, I would not put any differential equations
18 up, so if you were expecting any I'm sorry, although
19 I do have one, I do have one that sort is a derived
20 function.

21 When we talk about long half lives in
22 pharmacokinetics, we are usually talking 24, 36, 72
23 hours. Clearly, you know, etretinate, with 120 days,
24 the mean half life is a very extremely long half life,
25 and there's very few drugs we normally handle with

1 this long half life.

2 Again, by comparison, acitretin, which is
3 the active form, I'm sorry, which is the metabolite of
4 the parent, much shorter half life, and cis-acitretin,
5 which is the true active form, because, of course, the
6 earlier structures I showed you were plainer
7 structures and these things do have three-dimensional
8 shapes, the cis form, which is the true active form,
9 held a slightly longer half life than acitretin, but
10 really in comparison to 120 days is really
11 insignificant in terms of a half life.

12 And, we're talking about half life, it's
13 what's the concern of half life? Why are we keying in
14 on that as a factor? And, the factor is that we are
15 looking at total body loads, we are looking at how
16 much drug the body is going to store, and how long is
17 it going to take the body to get rid of that amount of
18 drug.

19 And, that can be derived from a
20 relationship of dose rate constant and dosing
21 interval, and if we take etretinate, and we use a
22 standard 50 milligram dose as is provided for in the
23 label, you can see that the total body store at steady
24 state is going to be around 13,000 milligrams. By
25 comparison, for Soriatane, the amount of Soriatane

1 that will be stored, assuming again a 50 milligram
2 dose, once daily dosing, is much lower, around 176
3 milligrams, because of the much slower elimination
4 rate for etetrinate in comparison to Soriatane, you
5 are going to produce very large body stores normally.

6 Now, the situation we have here is somewhat
7 different in the fact that we are going to be
8 accumulating drug, we are not going to be giving 50
9 milligram doses, you know, it's going to be a fraction
10 of this pool is going to be converted into etretinate,
11 but then, again, because it has such a much longer
12 terminal elimination, its rate of elimination is so
13 much longer, it will build up to appreciable stores,
14 even with low amounts of conversion, a low amount of
15 conversion but with a long half life it will build up.
16 That's a principle of accumulation.

17 And, you can see that, you know, this is
18 why, you know, we even think a post-contraceptive
19 period is possible with acitretin versus etetrinate.
20 If you were giving etretinate, and you accumulated,
21 you know, assuming 50 milligrams a day, to get rid of
22 that 13,000 milligram total body store would take a
23 very long time. With acitretin, a much lower total
24 body store, it's much more feasible to eliminate it
25 given its half life and all the other parameters

1 involved.

2 And certainly, even though we are forming
3 the longer half life component through this back
4 metabolism, still, we are not producing body stores
5 similar to what you would see if you gave the parent
6 drug itself.

7 How much, you know, if you were to ask me,
8 well, given you are talking about a total body store
9 of 176 milligrams for acitretin, how much of that
10 would be converted to etretinate, I cannot tell you
11 because we do not know all of the factors which go
12 into that situation.

13 What we do know, and we'll go through this
14 real quickly here, is this is the relationship between
15 multiple half life here at the bottom, one, two,
16 three, up through eight, and a fraction of the drug
17 that's been either eliminated or a fraction of steady
18 state. And, you can see, obviously, your one half
19 life, 50 percent is eliminated, two half life is up to
20 75 percent, and it goes up as its function. This is
21 not a curve that's related to Soriatane or any other
22 drug, this is a pharmacokinetics principle of half
23 life.

24 Basically, as a kineticist, we like to look
25 at what's 90 percent or 99 percent elimination, how

1 long does it take for that to occur. Usually, that's
2 somewhere around three and around six half lives,
3 three for 90 percent and six for 99 percent.

4 And, if we go and look at that, how does
5 that play out, assuming we are looking at etretinate,
6 you know, I've provided a table here which shows a
7 multiple half life fraction elimination, time in days
8 and time in years, if one looks at multiple half life
9 of three, 87, roughly, 90 percent eliminated, it comes
10 out, it would take you 540 days or one and a half
11 years.

12 If you were looking at 99 percent
13 eliminated, trying to reduce the risk, trying to
14 reduce the levels as much as you possibly could, you
15 know, it's 1,080 days or, roughly, three years.

16 Now, this, of course, is based on using a
17 half life of 180 days, and there's a lot of concern an
18 da lot of debate about what is the appropriate half
19 life to use, because, certainly, there are a number of
20 ones available.

21 Where do we come up with the "at least
22 three years" recommendation? Again, I have to
23 confess, it is pharmacokinetically derived, it's
24 pharmacokinetically driven, based on the principles of
25 half life, and it's based on some assumptions. It

1 assumes that the formation of etretinate from
2 acitretin requires the presence of ethanol and that
3 it's not a continuous process, that once ethanol
4 levels drop below some amount the process will stop,
5 that ethanol has to be there. It also assumes that
6 the total body load of accumulated etretinate formed
7 from acitretin will be lower than that formed from
8 the continuous administration.

9 We feel pretty good about that number two
10 is a pretty solid number, in the fact that in the
11 single dose study you gave 100 milligrams of
12 acitretin, you got the area associated with five
13 milligrams. Now, does that mean there's a 120th
14 conversion? No, it doesn't mean that, but it does
15 give us some feel for the fact that it's not a total
16 conversion, it's not a very large conversion. But,
17 what you should draw from that study is a conclusion
18 that there is a conversion and the actual quantifiable
19 number I don't think is very well know from that one
20 study, and I would not want to hang my hat on that
21 number.

22 It also assumes that ethanol is the only
23 species that can participate in this reaction. That
24 is not really know for certainty. There's certainly
25 other two carbon fragments, the question of how

1 acetaldehyde interacts, any other species interact and
2 form etretinate or similar compounds, that is not
3 known. Again, there's room, I think, here for some
4 more in vitro work in that area, trying to look at
5 these different factors.

6 Again, the half life of etretinate is
7 variable. You know, certainly depending on what
8 reference you want to look at, you'll get different
9 ranges, different means. The problem is, is that as
10 a kineticist I can tell you with a short half life
11 drug, I can very easily tell you the half life. A
12 drug with a two hour half life, you know, I can sample
13 for 24, 48 hours, take as many samples as I want, and
14 get a very good estimate of half life. The problem
15 with drugs with very long half lives, especially one
16 approaching six months, is that if you look at the
17 regulations in the CFR, it talks about following
18 terminal elimination rate out to three to five half
19 lives to get a good estimate, that means you are going
20 to be bringing patients for years. It doesn't happen.
21 The n starts dropping off, it gets very small, there's
22 fluctuations, especially if you have a patient who is
23 somewhat obese and was in your trial, then goes on a
24 diet and starts mobilizing fat stored, there's all
25 sorts of things that happen, and, really, the mean

1 number I don't think is one we should be focusing on,
2 because either you can choose the mean or you can
3 choose the median, which is somewhat less than 120
4 days, but still, we are talking about exposing a lot
5 of people on the upper side of it to some degree of
6 risk, some degree of exposure.

7 We have chosen our calculations to be
8 somewhat conservative, and there are criticisms of it,
9 but I think that it's a safer approach to take, that
10 we chose -- the sponsor chose to use a value of 120
11 days, which would make 99 percent elimination occur
12 within two years, we chose to use 180 days. It's
13 somewhat higher than the upper limit that's been seen
14 so far, 168 hours -- sorry, 168 days is about the
15 longest half life we've seen, but again, those half
16 life determinations are not as accurate as they are
17 with shorter half life drugs.

18 One hundred and eighty days builds in some
19 conservative numbers, it also is somewhat
20 calculationaly easier to deal with in some ways, and
21 it gives us the three year recommendation.

22 The "at least three years" recommendation,
23 why at least three years? Again, part of that goes
24 back to the uncertainty in the calculation of the
25 numbers. We want to be able to put it in the label in

1 a pharmacokinetics context, such that the physician
2 can discuss with the patient, and a patient can make
3 an informed decision, as to how they feel about the
4 drug, how they feel about these various factors. It's
5 really being put in there as a guidance, because,
6 quite frankly, we do not have -- I do not feel we have
7 enough data to really say this is an absolute number.
8 It's a measure of the certainty and the uncertainty
9 that we have.

10 We cannot guarantee, and I think that we'll
11 see some examples later today, and in your packet for
12 those of you who have read ahead, there are some
13 patients in certainly the background materials who
14 much longer than three years still had levels of
15 etretinate circulating and also in their fat tissue.
16 This reflects both extensive body sequestration, body
17 composition, alcohol consumption. Alcohol consumption
18 certainly is going to be a factor here, the more you
19 drink, the more you are going to convert, the larger
20 body store you are going to produce, enzyme activity,
21 and also, quite frankly, there's also the specter of
22 unknown mechanisms, because we don't know with 100
23 percent certainty that alcohol is the only species
24 that participates in this reaction. Certainly, we
25 know it participates, and we know it's probably the

1 most likely candidate, but there's also the
2 possibility that some other species could also
3 interact.

4 And, with that, I'd like to close the
5 pharmacokinetics section of the presentation and turn
6 it back over to Doctor O'Connell.

7 CHAIRMAN McGUIRE: Are there questions from
8 the committee? Yes, Doctor Kilpatrick.

9 DOCTOR KILPATRICK: Excuse me, Dennis.

10 MR. BASHAW: Yes, sir.

11 DOCTOR KILPATRICK: As a statistician, I'm
12 naturally interested in the design of the studies in
13 which you are reporting, specifically, were these in
14 vivo or in vitro? I mean, I'm talking about PK-2
15 through PK-6, all of that, is that based on --

16 MR. BASHAW: In vivo.

17 DOCTOR KILPATRICK: -- in vivo.

18 MR. BASHAW: Yes, sir.

19 DOCTOR KILPATRICK: And, were they men or
20 women?

21 MR. BASHAW: Mixed population.

22 DOCTOR KILPATRICK: And, what was the
23 sample size?

24 MR. BASHAW: I believe for the alcohol
25 interaction study, I believe it was 20 subjects. I

1 don't have that number right off the top of my head,
2 but I believe --

3 DOCTOR O'CONNELL: Ten.

4 MR. BASHAW: -- ten, I'm sorry, ten, it was
5 ten subjects.

6 DOCTOR KILPATRICK: Ten subjects, five men
7 and five women?

8 MR. BASHAW: I don't think it was quite
9 that evenly broke down.

10 DOCTOR KILPATRICK: But, of that order.

11 MR. BASHAW: Six and four, yes.

12 DOCTOR KILPATRICK: Okay.

13 You can probably see where I'm coming from.
14 I'm concerned very much with the point that is made in
15 Doctor O'Connell's talk about these being theoretical
16 or deterministic estimates, and, basically, we have
17 very little handle on the intrinsic variability of
18 individuals. You mentioned some of this, like
19 obesity, or changing of weight, and different diets,
20 but, basically, we know nothing about the
21 subpopulations, there may be subpopulations at risk,
22 as you mentioned in terms of racial composition, et
23 cetera. So, my concern is that, not that you are
24 being conservative, but that you are being too
25 liberal, frankly.

1 MR. BASHAW: Well, that's something we've
2 wrestled with, and, you know, clearly, we did not
3 believe that we had a determinate, we could say three
4 years absolute, two years absolute, we felt that we
5 had this data which is suggestive, certainly, in
6 nature, but certainly is not definitive, and we
7 certainly think there is room for additional work.

8 You know, in terms of trying to come up
9 with a reasonable time frame that would allow for the
10 marketing of the drug, would allow for the clinical
11 use, that was where we came and developed the "at
12 least three years," and, again, trying to develop
13 labeling and materials that would put this in some
14 perspective for the physician, for the patient, that
15 would say, well, here are some various factors. You
16 know, if you've not drunk, if, you know, your body
17 size is such, you know, these factors will go into
18 play.

19 But, clearly, you know, it's not intended
20 to be, we do not have, I do not believe, deterministic
21 data here.

22 CHAIRMAN McGUIRE: Doctor DiGiovanna.

23 DOCTOR DIGIOVANNA: Actually, I have three
24 questions. The first is, do you have any idea where
25 in the body this esterification takes place, whether

1 it takes place in the liver, and only in the liver,
2 whether it's possible for it to take place in the fat,
3 in the area of body storage of etretinate and, to some
4 degree, acitretin?

5 MR. BASHAW: We know that, from some of the
6 in vitro work, that coenzyme QA is involved in it. I
7 believe it's mostly in the liver, not in the fat, the
8 partitioning of acitretin into the fat is very poor.
9 I mean, the really short, relatively compared to the
10 parent drug half life being that way.

11 Could there be some out there, certainly
12 there could, but I don't believe that's the primary
13 site.

14 DOCTOR DiGIOVANNA: But, its half life
15 coming out of the fat might be longer than its half
16 life coming out of the serum.

17 MR. BASHAW: Yes.

18 DOCTOR DiGIOVANNA: What I'm saying is,
19 when one considers the time or the amount of acitretin
20 that's at risk for conversion into etretinate, one
21 would say if it's only when it is passing through the
22 liver that's one window of time, but if it's also the
23 time that it may be in the fat, then that may be
24 longer than the half life of, I think, 50 hours.

25 MR. BASHAW: Yes, this is true.

1 DOCTOR DiGIOVANNA: The other question is
2 that, there is further metabolism, I believe, of
3 acitretin to a variety of other compounds which are
4 present at lower concentrations, and whose activity is
5 really not known, either as an agent of efficacy or an
6 agent of teratogenicity, and I wonder if there is any
7 information on esterification of other derivatives
8 that may be present.

9 MR. BASHAW: Well, you hit on one of the
10 key questions we've always been concerned about,
11 because obviously there are other primary alcohols,
12 one, two, three, four, how many carbons you want to
13 attach on there, and other alcohol-like esters and
14 other things that could possibly interact.

15 We do not know, we do not know honestly, to
16 my knowledge.

17 DOCTOR DiGIOVANNA: And, the final question
18 that I have is that you mentioned that cis-acitretin
19 was the true active metabolite, and I would take issue
20 with that for a variety of reasons, one of which is
21 something I fully intended to bring with me today and
22 managed to fail to do that, and that's an article in
23 the British Journal of Dermatology within the last two
24 or three months, showing that patients with a variety
25 of different diseases, who failed to respond to

1 acitretin therapy, did respond to etretinate therapy.

2 So, there may be other active metabolites.

3 MR. BASHAW: Oh, certainly, and the parent
4 itself may have its own inherent activity, too.

5 DOCTOR DiGIOVANNA: Yes, I don't debate
6 that.

7 CHAIRMAN McGUIRE: Doctor Lammer?

8 DOCTOR LAMMER: When you say that there's
9 an undetectable level of the drug, that assumes a
10 certain level at which you can detect the drug. And,
11 you didn't actually mention that in your presentation.
12 For example, when you talked about that there's no
13 evidence for conversion without alcohol ingesting of
14 acitretin to etretinate, that's only based on what
15 level of being able to detect the chemicals?

16 MR. BASHAW: I believe that level is one
17 nanogram per mil, I believe that's what it went down
18 to in that study. I'm looking -- .1 okay, .1.

19 DOCTOR LAMMER: What was the assay that was
20 used for the research?

21 CHAIRMAN McGUIRE: Excuse me, the
22 information and the aside comments are important, and
23 they need to be transcribed, and we need to make our
24 comments with the microphone. Yes, Bob.

25 DOCTOR ARMSTRONG: I'd just like to clarify

1 that the quantification limit on the assay used in the
2 alcohol interaction study was five nanograms.

3 MR. BASHAW: That's important to know,
4 because several of the case reports of women who have
5 had babies with birth defects, who have gotten
6 pregnant about a year after they stopped taking
7 etretinate, had blood levels around that level, so
8 that, I think that's relevant to the discussion, to
9 know that there's concern about teratogenicity at the
10 level -- at blood levels that are close to the range
11 of detection of these assays.

12 CHAIRMAN McGUIRE: I'd like to ask a brief
13 question. Are there ways to facilitate or to drive
14 the de-esterification of the compound?

15 MR. BASHAW: I'm sorry, I don't understand
16 your question.

17 CHAIRMAN McGUIRE: Well, the moiety that's
18 most easily excreted is a non-esterified moiety.

19 MR. BASHAW: Oh, okay, you are saying --

20 CHAIRMAN McGUIRE: And, if you could
21 chemically drive the de-esterification, if you could
22 de-esterify.

23 MR. BASHAW: Okay, run it to completion.

24 CHAIRMAN McGUIRE: Yes.

25 MR. BASHAW: Okay.

1 There is not -- we are not aware of
2 anything that will do that, no, not in in vivo.
3 Certainly, in an in vitro system one could do
4 different things, but in terms of in vivo, I don't
5 believe there is anything to that.

6 CHAIRMAN McGUIRE: Are there other
7 questions?

8 DOCTOR CANTILENA: Yes, I just have one.

9 Hi, Dennis, sorry I missed the bulk of the
10 presentation, I've been flipping through your slides
11 here. Can you just talk about, from, again, a
12 chemistry basis, you know, what other types of things
13 in the food chain -- excuse me, in the diet, would,
14 other than ethanol from a chemical basis, be possible
15 candidates.

16 MR. BASHAW: Well, that's a great question.
17 There's a possibility, certainly, of acetaldehyde and
18 some of the other aldehydes, other primary alcohols,
19 I mean, certainly, we know that ethanol is formed in
20 the metabolism of certain sugars. In terms of direct
21 contributors, we don't really have a good list of
22 that. That's where, I think, again, is one of the
23 areas where future research needs to be pursued,
24 because as was brought up, are we only concerned about
25 two carbon fragments, or three carbon fragments, or a

1 range. Certainly, this is an active site that's
2 suitable to some metabolism.

3 And, under the right conditions, we are
4 forming these other species that have much longer half
5 lives, and the concern is that even if it is formed at
6 very low rates, below limits of detection, that
7 eventually those levels, because of its long staying
8 power, will build.

9 CHAIRMAN McGUIRE: Ms. Cohen?

10 MR. BASHAW: We'll go together later, Lou,
11 if you have any questions, I'll be happy to go over it
12 with you.

13 MS. COHEN: Are there any examples of other
14 drugs where people have to abstain from having
15 relations? This is really about people, and I'm
16 hearing all about the drugs, but this is depending
17 upon people to abstain, and I think AIDS is a
18 wonderful example, where people know if they engage in
19 sex and they have AIDS someone can have a problem.

20 We are expecting people to lead a totally
21 different kind of life, to abstain if they have to.
22 We have people who might not disclose in their
23 relationship with someone else that they've taken this
24 medication, it's a lot about the human psyche that we
25 are talking about. You can talk about the medication,

1 but we're expecting people to do all kinds of things.

2 And, do we have an experience, which I
3 don't know about, obviously, where people have had to
4 abstain in their life, and do they do it?

5 You can say all you want about that, but if
6 you have people who don't really want to do things,
7 and do things impetuously, they drink too much in an
8 evening and they forget all about what they've been
9 taking, I need to know more about what people are
10 about in this issue.

11 CHAIRMAN MCGUIRE: I think this will be
12 addressed later by the sponsor. Roche has an enormous
13 experience with 13 cis-retinoic acid.

14 Although to be sure, the exposure is quite
15 a bit shorter, we are dealing with a five month
16 exposure, and compliance I think has been good. Each
17 of us who uses 13 cis-retinoic acid in a clinical
18 setting signs off on a fair amount boilerplate and the
19 patient is a participating partner in the enterprise.
20 And, the experience with that, at least in the short
21 run, has been good.

22 MS. COHEN: But, that's in a clinical
23 setting, but I know among young people, it's something
24 that's good for me, you want to give it to your friend
25 and let your friend use it, and it could be the

1 sharing even of this medication, where it's under no
2 supervision whatsoever.

3 CHAIRMAN McGUIRE: Okay. I think you have
4 me on the defensive. These are people we are
5 treating, and these are young, active people who are
6 in the process of getting engaged, getting married,
7 meeting other friends, and having a full life.

8 The contract is very, very clear.

9 Doctor Lammer.

10 DOCTOR LAMMER: I'd really like to comment
11 on that, because I attended the Advisory Committee
12 hearing at which it was deliberated about whether to
13 approve etretinate or not, and my clear memory from
14 that meeting was that this was presented -- etretinate
15 was presented as a medication that would be used and
16 limited to women with severe pustular types of
17 psoriasis, and for whom, unlike Acutane, women treated
18 with this medication for that condition did not have
19 prolonged periods of remission off therapy.

20 And, at that time, I felt like the
21 committee was told and reassured that the teratogenic
22 effects were unlikely, because women who had the
23 disease for which they were being treated with this
24 drug were so sick that it was unlikely that off
25 therapy for a period of several years that they would

1 be healthy enough to conceive and to bear children.

2 I think that really bears to the question
3 you are asking, and I would like to see that question
4 addressed today as well, because when etretinate was
5 approved, the way it was presented, the patient
6 population for whom this drug was targeted, was that
7 this was not likely to be a group of women who would
8 ever be healthy enough to bear children anyway. And,
9 I think it would be helpful to know if that's still
10 the intent of the study -- or the clinical population
11 for whom this version of the drug is intended.

12 CHAIRMAN McGUIRE: Doctor Wilkin, did you
13 want to respond to that now or later?

14 DOCTOR WILKIN: I think maybe it might come
15 in some of the slides that Doctor O'Connell is going
16 to present in the next few minutes.

17 DOCTOR O'CONNELL: I agree. I think a lot
18 of these issues will be addressed as we go through the
19 information we have available, and then at the end of
20 all the presentations, as I said earlier, Doctor
21 Wilkin is going to go through the thinking process,
22 the philosophic process that addresses a lot of these
23 issues.

24 As Doctor Bashaw has just pointed out, and
25 several participants have alluded to, the

1 pharmacokinetics data about half life tells us that
2 after six half lives approximately -- well, close to
3 99 percent of any etretinate that's formed should
4 theoretically be eliminated.

5 And, clearly, for a clinician to use that
6 information, it would be very helpful to know, as
7 Doctor Lammer alluded to, what is the threshold
8 concentration for the teratogenic risk. And, here,
9 as in many places, what you'll see as we go through
10 the data, we entirely agree with the sponsor that the
11 threshold concentration for the teratogenic effects of
12 acitretin are simply not known. We entirely agree
13 with that.

14 And so, basically, what we are left with is
15 the third item that I had on my list, which was to
16 look at the available clinical data and ask, what does
17 that tell us, what can we learn from that to help us
18 with this important decision?

19 And, essentially, if we look at the
20 clinical data, we have three bodies of information
21 that we can examine. One pertains to the persistence
22 of the etretinate or the acitretin in vivo. The
23 second thing we can look at is the pregnancy outcomes,
24 and the third thing that we need to consider is the
25 spectrum of congenital malformations that may be

1 associated with retinoid exposure, in other words,
2 what are we looking for when we look at the outcome
3 data, what do we see there that sends up antennas or
4 tells us to be reassured?

5 As far as the persistence question goes,
6 again, we are in entire total agreement with the
7 sponsor that this is a critical question, and it's
8 absolutely essential to formulating at some point a
9 definitive label to know how long these substances can
10 be found in the bodies of women of reproductive
11 potential.

12 And, we also further agree with the sponsor
13 that the data that are available right now really
14 don't fully answer that question, as Doctor Bashaw has
15 pointed out, the studies that have been completed
16 don't completely rule out the possibility that
17 measurable concentrations would be formed until
18 multiple dose therapy with acitretin, even when
19 alcohol is prohibited.

20 So, basically, then what we come to is,
21 what do we know, what information do we have about
22 persistence, and this is in addition to the
23 information that Doctor Bashaw just presented with the
24 ten patients that were dosed with high levels of
25 ethanol and given the acitretin concurrently.

1 From studies of patients in the European
2 market, we do know that about 16 percent of the
3 patients taking Soriatane, these are patients who were
4 not taking etretinate, did have measurable etretinate
5 levels. Now, this was not over time, this was not
6 looked at after they had stopped the therapy, and
7 there was no -- we don't know, you know, how much
8 alcohol did these patients drink, it's just these are
9 patients who had etretinate levels.

10 However, there's a second study that this
11 sponsor did, where they took women who were being
12 treated with acitretin for medical reasons, because
13 they needed it, and they looked at how long after they
14 stopped the therapy did they have measurable levels of
15 acitretin and etretinate in their plasma, as well as
16 in their fat. They took biopsies of subcutaneous fat,
17 and I'm not going to discuss the patients who had
18 etretinate levels while they were taking acitretin,
19 this is the subset of those patients, 23 who were
20 looked at over time.

21 Three of the 23 patients post-therapy did
22 have measurable levels of etretinate. All three of
23 these patients did note that they had consumed various
24 amounts of alcohol during the treatment with the
25 acitretin. In one of these patients, the alcohol

1 intake was quoted as sporadic or moderate, but that
2 patient had etretinate levels in plasma and fat 52
3 months, that's not weeks, that's months, after
4 stopping acitretin therapy.

5 So, I think that this data suggests that
6 what Doctor Bashaw was alluding to is absolutely
7 correct, that the pharmacokinetics data is largely
8 theoretical in the sense that there's great
9 variability, and there's many things we don't
10 understand about this process at the current time.

11 Now, the next thing that I'm going to
12 discuss, this is the last thing on my list, which was
13 the pregnancy outcome data. And, before I go to that,
14 I wanted to point out two things. I'm going to be
15 referring to cases that were prospectively reported
16 and cases that were retrospectively reported, and I
17 just want to define quickly what I mean by that.

18 Prospectively reported means that the
19 doctor called the sponsor and said, this pregnancy has
20 occurred, and they called the sponsor and told them
21 that before they knew the outcome. Okay.

22 Retrospective reports mean that the doctor
23 calls the sponsor after they know the outcome and
24 says, look what happened. And, I don't think there's
25 any question that we all recognize that

1 retrospectively reported cases are, by definition,
2 biased because it's just human nature, people report
3 bad news more than they report good news.

4 Now, having said that, I also want to point
5 out that Doctor Armstrong, the focus of his talk is
6 really going to be on the pregnancy outcome data, and
7 there was an update in the accuracy of that data in
8 the last couple days. So, if there's a slight
9 discrepancy between my numbers and his numbers, his
10 numbers are the right numbers.

11 It doesn't affect the point of why I am
12 also presenting this data. I'm not going to present
13 it in the detail that Doctor Armstrong is going to
14 present it in, but at the end you'll see that the
15 point of my presentation is, the small discrepancy
16 doesn't make any difference.

17 So, if we go to the pregnancy outcome data,
18 first let's look at the prospective reports available
19 for acitretin. And, 38 of these prospective reports
20 had a known outcome, so the outcome is known.
21 However, the other half, the other 48, we don't know
22 the outcome. Eleven of these cases are coded as lost
23 to follow-up, 31 were coded as no information
24 available, and six were coded as pending.

25 If you looked at the ones that were coded

1 as no information, 97 percent of those cases were
2 abortions, so this is basically a knowable
3 information, because elective abortion generally
4 destroys the evidence of embryopathy, and the other
5 problem is that retinoid exposure may be a -- that
6 really should be a may more than it is, may be a risk
7 factor for spontaneous abortion. So, we don't really
8 know anything about half of the prospective reports.

9 Now, if we do look at the pregnancy outcome
10 in the five prospective reports where abnormalities
11 were reported, so this is the pregnancy was reported
12 to the sponsor before the doctor knew what the outcome
13 was. And, the order here is in the order for the
14 committee members that have the actual data, it's in
15 the same order as it is listed in the data, so you can
16 follow it.

17 In these cases, the only one that
18 represents a congenital malformation that is
19 recognized as possibly one of the things that you
20 might see as part of the whole expression of the
21 syndrome would be the craniofacial syndrome, and,
22 unfortunately, in this case the information isn't
23 available to tell us how long after the patient
24 stopped taking the drug conception occurred. So, the
25 prospective data doesn't cause concern as such, but it

1 doesn't reassure us, because the number of cases is so
2 small or the information is incomplete.

3 If you then go and look at the
4 retrospective reports for acitretin, and this is,
5 again, not during treatment, but this is cases where
6 the conception occurred after the patient had stopped
7 the drug, again, if you look at the list of how the
8 congenital malformations or abnormalities were
9 reported, there is the deformity skeletal, Turner's
10 syndrome, an unspecified malformation, a heart defect,
11 a heart defect, chromosomal disorder, a heart defect,
12 dystroph ossification and a premature birth. So, the
13 nine retrospective reports, basically, the issue comes
14 down to, as I alluded to earlier, when we look at
15 these reports it's not for incidence, it's for a
16 pattern, and it's not clear to us at this time what it
17 is exactly that we are looking for here, and I'll
18 allude to that in a few minutes.

19 So, if we then say, well, how can we get
20 more data, we can look at etretinate, because the drug
21 actually that we are worried about down the road here
22 is etretinate, not acitretin, because it's etretinate
23 that persists. And, here there are 18 prospective
24 reports where the conception occurred greater than two
25 years after the drug was stopped, and, again here,

1 there were seven normal outcomes, five unknown
2 outcomes, and three that were coded as abnormalities,
3 again, none of these are the classic retinoid type
4 syndrome complex that you see.

5 If you look at all the cases for etretinate
6 and acitretin, and this is all prospective and
7 retrospective, if you look at all the cases where the
8 exposure was 18 to 24 months there's 41, and here, 15
9 were coded as normal, 17 as unknown, and nine as
10 abnormal. The ones that have the P after them mean
11 they were prospectively reported, the ones that have
12 the R were retrospectively, so there was one case
13 prospectively reported of an absent hand/wrist, one
14 case prospective of an undescended testicle, and I
15 think Doctor Armstrong will discuss, this may be one
16 of the cases that was coded twice. There were four
17 premature births, two which resulted in death. There
18 was a retrospective eye malformation, a retrospective
19 tetralogy of fallot, and a retrospective multiple
20 malformations cardiac abnormality.

21 And then the other way to get more
22 information is the same principle, is to just look at
23 etretinate and acitretin greater than 24 months,
24 because there's so few cases for acitretin after 24
25 months, and there if you group them together there's

1 29 cases, normal outcome in ten, unknown in ten, so
2 again, half the cases there, or at least the same
3 number as normal and unknown, and then abnormalities
4 reported in nine of the cases, again, the P is
5 prospectively, the R is retrospectively. And, again,
6 here we have retrospectively a malformation that we
7 don't really know anything about, aplasia of the
8 forearm, a still birth, a heart defect, a heart
9 defect, and then, of course, the chromosomal disorder.

10 And, the last point I want to make about
11 this data, because as I said Doctor Armstrong is going
12 to present this data more thoroughly in his
13 presentation, is that this is another instance where
14 we agree with the sponsor that for the acitretin data,
15 specifically, there just isn't enough information.
16 There has just been very limited information that's
17 come in.

18 I think the bottom line with just the sort
19 of quick overview I've given you of the pregnancy
20 outcome data that's available, is that we see three
21 problems. One, there's a lot of missing information
22 of outcomes that we just don't know anything about.
23 There's also not a lot of prospective cases here to
24 look at, and for the retrospective cases it's really
25 not clear to us what it is that we should be looking

1 for.

2 And, that, in fact, is the reason why we
3 invited Doctor Lammer to come speak to us today, to
4 address the question of birth defects of the retinoid
5 syndrome type, what it is, perhaps, that we should be
6 looking for here.

7 But, before we go on there, I just want to
8 show one more slide, and that is to reiterate what
9 Doctor Bashaw referred to as our proposed label, which
10 speaks to the wording, "at least three years."

11 Doctor Wilkin, at the end, will discuss the
12 thinking that went behind the choice of this wording,
13 the rationale. We feel that this label avoids a
14 definitive statement, which we cannot support right
15 now with the currently available information, that it
16 places the teratogenic risk into some sort of temporal
17 perspective to give some guidance to patients and
18 physicians based on the pharmacokinetics data that
19 Doctor Bashaw discussed. And, we also think that this
20 type of label encourages individualized decisions
21 regarding risk and benefit.

22 So, I think I'll stop there.

23 CHAIRMAN McGUIRE: Are there questions for
24 Doctor O'Connell?

25 Doctor Lammer.

1 DOCTOR LAMMER: Comments, a comment really,
2 more than a question. I can't agree with some of your
3 interpretation, and I recognize that I don't expect
4 that you would be able to interpret all of those
5 reports, but a number of the things up there are
6 consistent with effects from developmental toxicity
7 from retinoids, such as hypotonia is a classic
8 neurological deficit that these children have, and
9 also some data indicating that the risk of premature
10 birth is doubled from the use of 13 cis-retinoic acid
11 during pregnancy. So, those are both clearly adverse
12 outcomes that have been statistically associated with
13 exposure to the drug, and really are part of the
14 typical features.

15 I think one lesson we've learned is that,
16 because we have both a retrospective case series of
17 children with retinoid embryopathy, and a group of
18 children with malformations and adverse outcomes from
19 a prospectively followed cohort of exposed
20 pregnancies, by comparing those two populations we can
21 really describe the whole spectrum of effects. And,
22 when you are looking at a prospectively followed
23 cohort, you are much more likely to see more mild
24 effects of -- the mild end of the spectrum of effects
25 of retinoid embryopathy, and you would much less

1 commonly expect to see this triad of major
2 malformations that's been described by a number of
3 people.

4 DOCTOR O'CONNELL: Well, I appreciate your
5 comments, because maybe I didn't make myself clear.
6 I was referring to the defects that we would -- that
7 are classically commonly recognized as parts of the
8 defined syndrome, and I guess the point I was trying
9 to make is that we don't know if that's the right way
10 to look at that retrospective data, and that's why we
11 invited you.

12 DOCTOR LAMMER: Okay.

13 CHAIRMAN McGUIRE: Are there other
14 questions for Doctor O'Connell?

15 Thank you.

16 DOCTOR O'CONNELL: Thank you.

17 CHAIRMAN McGUIRE: Doctor Lammer, you are
18 next, Doctor Lammer from Oakland Children's Hospital.

19 DOCTOR LAMMER: Mr. Chairman and members of
20 the committee, I'm a pediatrician with training in
21 medical genetics and epidemiology, and I'm the
22 Director of the Medical Genetics Program in the
23 Craniofacial Anomaly Center at the Children's Hospital
24 in Oakland, California.

25 I have been involved with research in this

1 area, primarily, with describing the natural history
2 of developmental toxicity from 13-cis retinoic acid,
3 the brand name Acutane, since about 1984, and I've
4 attended a handful of these Advisory Committee
5 meetings when issues have come up about the
6 developmental toxicity of both 13-cis retinoic acid
7 and etretinate.

8 Today, I was invited to this hearing by the
9 FDA staff. I didn't really seek out this opportunity.
10 I have to tell you, I'm here with a great deal of
11 trepidation, because my previous experiences in
12 dealing with this Advisory Committee on issues of
13 trying to prevent retinoid induced toxicity to
14 children have left me so profoundly disillusioned with
15 the regulatory process and the purpose of the research
16 that I've been doing that I, basically, left the
17 research field and am pretty minimally involved these
18 days. So, I'm primarily a clinician and administrator
19 now, but I am involved still in some collaborative
20 projects with Doctor Jane Adams in continuing to
21 follow up children whose mothers accidentally used
22 Acutane when they were pregnant.

23 Could I have the first slide? I know I
24 presented this data to the committee before, much of
25 it, but for those of you who have not heard of it,

1 because I know the committee's composition has
2 changed, I'll try to summarize the findings of our
3 research in general, and I recognize from one of the
4 previous questions, there's more epidemiologic
5 expertise on the committee than I assumed, and I'll
6 try to provide a little more detail than on my slides.

7 We, basically, studied two populations of
8 children. One are children who are reported to us
9 retrospectively, who have malformations or
10 neurological problems, et cetera, related to their
11 mother's use of isotretinoin during pregnancy. We
12 also follow, and the data I'm going to present is
13 really from our cohort of prospectively followed women
14 who have used this drug during pregnancy, so that's
15 the second study population that we tracked.

16 The first population, who were
17 retrospectively reported, give us a good idea about
18 the severe end of the spectrum of adverse effects, and
19 studying those children has been useful, I think, for
20 trying to understand better, primarily, the
21 pathogenetic mechanisms through which this drug might
22 have its effects.

23 In contrast, the group I'm going to present
24 are outcomes from a prospectively followed cohort of
25 women who have used this drug during pregnancy. That

1 group allows us to quantify risks for a number of
2 adverse outcomes of pregnancy that I have listed on
3 this slide, and gets us the whole spectrum of adverse
4 effects from the mild to the severe.

5 So, we started this study in 1984. It
6 originally was funded by two grants from Hoffmann-La
7 Roche, now we have support from the NICHD to continue
8 this research, but, basically, the purposes were to
9 quantify risks for spontaneous abortion, major and
10 minor anomalies, hormonal deficiencies, and that gets
11 to the question of some data which was just presented
12 showing that one of the case reports reported a child
13 with hypocalcemia, which is a retinoid-related adverse
14 outcome of pregnancy in an infant, sensory deficits,
15 hearing and vision, effects on post-natal growth and
16 prenatal growth, and making correlations between dose
17 and timing and of exposure of use of the drug and the
18 various adverse outcomes. And then lastly, we are
19 interested in knowing what information about how these
20 women happened to get pregnant while using the drug,
21 with the idea of trying to prevent these tragedies
22 from happening to other families.

23 Our second study, which is still ongoing,
24 is a longitudinal assessment, especially focusing on
25 children who are exposed to Acutane during pregnancy,

1 but who are apparently non-malformed at birth, to see
2 what kind of adverse effects this drug might have on
3 behavior, intelligence and socialization issues,
4 again, tracking their longitudinal growth, assessing
5 their teeth and orthodontic development, et cetera.

6 We've got a wide range of studies of
7 outcomes of these children, ranging from having
8 collected exfoliated baby teeth from a number of them,
9 getting dental and radiographic and orthodontic
10 studies as they've gotten older, and our current
11 ongoing project studies their school performance and
12 behavioral and intellectual functioning at age ten.
13 So, we've tracked this group of children
14 systematically until they are at least ten years old,
15 and some of them even beyond that point.

16 The cohort is basically defined by women
17 who used Acutane between the conception and 60 days
18 after conception. We've also studied about 15
19 pregnancies in which women started using this drug
20 more than 60 days after conception, but I'm only going
21 to show a picture of one child from this group today.
22 I'm primarily focusing on this cohort, and we've now
23 had data and have tracked about 140 pregnancies
24 prospectively, in which women have used Acutane, but
25 I'm only going to present the first 117, I think,

1 pregnancies, because I didn't have enough warning for
2 this meeting to relook at all of that data. My
3 eyeballing it is that the results really aren't going
4 to be that different with the increased numbers.

5 And, again, when we look at spontaneous
6 abortion outcomes, we look at this cohort a little bit
7 differently, in that the woman had to be identified to
8 our study before 13 completed weeks of pregnancy in
9 order for us to properly assess the risk for
10 spontaneous abortion. So, we limit the denominator
11 at-risk population for spontaneous abortion outcomes
12 to women who we ascertained in the first 13 weeks of
13 pregnancy.

14 And, again, to get into this cohort, the
15 woman had to be identified to us, and our reports
16 primarily come from obstetricians, Teratology
17 Information Services, Franz Rosa here at the FDA, the
18 Centers for Disease Control and a number of other
19 sources, and these women, we have to know nothing
20 about the outcome of the pregnancy. In other words,
21 these women had to be identified to us before any
22 prenatal diagnostic testing or other information about
23 the outcome of the pregnancy was known.

24 And, again, these are all, basically, women
25 who have acne and like many of the surveys have shown

1 only about half the women who were put on Acutane
2 actually have cystic acne, many of the women who we
3 have tracked who have gotten pregnant while using this
4 drug never had cystic acne to begin with.

5 Again, as I said, I'm going to present the
6 data on the first 115 pregnancies we've tracked.
7 We've lost very few of them, five out of 115 lost to
8 follow up, and a pertinent question that was raised
9 earlier, we eliminate women who have elected
10 terminations of pregnancy from participation in this
11 study, so this is only an inclusion of women who did
12 not elect to have a termination of pregnancy in this
13 study, and that may lead to some biases, in that we
14 think a high, high percentage of women who get
15 pregnant while using this drug choose to have a
16 termination.

17 So, 27 spontaneous abortions, these are the
18 live-borne children with exposure in the first 60
19 days. This is six prospectively followed children,
20 where the exposure began after day 60, and we're
21 tracking most of these children again until they are
22 quite old. Our participation rate is very high, more
23 than 90 percent.

24 So, in looking at the risk for spontaneous
25 abortions again, we've tracked 65 pregnancies. We

1 were able to identify before 13 completed weeks after
2 the last menstrual period date, five of those are ones
3 we watched to follow up, so of the ones we were able
4 to track 40 percent of those women went on to have a
5 spontaneous abortion. The spontaneous abortions
6 always occur by week 15, and, unfortunately, we've
7 done numerous attempts to find the embryopathology
8 studies on the products from these pregnancies and
9 have been universally unsuccessful in getting any
10 useful information.

11 So, we don't know what's wrong with these
12 pregnancies. We don't know whether these babies are
13 all severely malformed and exactly what the problem
14 is, but to put this into perspective, for clinically
15 recognized pregnancies the generally accepted
16 background risk for spontaneous abortion is 15
17 percent, so this is about a 2-1/2 -- two to 2-1/2 fold
18 excess risk for spontaneous abortion.

19 We have a control group that's identified
20 for this study by, they are basically age matched kids
21 randomly selected from the practice population of the
22 primary care physician for the child who was exposed
23 to the drug, so that's how we select our controls.
24 These children, by the way, are from more than 30
25 states, Canada and Puerto Rico, so we've traveled all

1 over North America to perform this study from 1984 to
2 1992, and now ongoing we've got the neuropsychological
3 studies being primarily directed by my collaborator,
4 Doctor Jane Adams.

5 So, basically, what we see is about a 300
6 gram mean difference in birth weight between children
7 exposed to Acutane in controls, and, basically, the
8 difference is due to an increased risk of prematurity.
9 Okay? So, 16 percent of the pregnancies lead to
10 premature delivery, and that's about double the risk
11 nationally for prematurity for all racial ethnic
12 groups combined, and that number is about eight
13 percent. So, basically, this drug, unlike many human
14 teratogens, does not cause intrauterine growth
15 retardation. The difference in birth weight is almost
16 entirely attributable to an increased risk for
17 premature delivery, and this is a statistically
18 significantly increased risk for premature delivery,
19 and this difference in birth weight is statistically
20 significant as well.

21 I should add that a fair amount of the
22 developmental toxicity of this medication is actually
23 due to the problems these children have from
24 prematurity, as much as it is the malformations that
25 the drug induces.

1 While this slide I've not corrected, but
2 needs to be corrected, basically, overall 77 children
3 all exposed between conception and day 60, 23 of those
4 babies were born with at least one major malformation,
5 and that's an extraordinarily high absolute risk for
6 major malformation. This is in a magnitude of risk in
7 terms of environmental exposures only comparable to
8 congenital rubella infection or thalidomide exposure.

9 Now, when we look at that group in terms of
10 when the mother used the drug, we found a very
11 interesting finding, and actually this needs to be
12 corrected, through a lawsuit we were finally able to
13 get -- not our lawsuit, but someone else's -- better
14 pharmacy records for this one case, and that case
15 actually turned out to have a later exposure. So,
16 actually now, we've tracked, this slide shows 25
17 pregnancies, we've now tracked close to 40 women who
18 stopped taking Acutane before 15 days after the
19 estimated date of conception. None of those babies
20 have major malformations. All of the risk is down
21 here in this group of women who continued to take
22 Acutane beyond the 14th day after conception, and that
23 risk is on the order of 35 percent chance that those
24 women would have a baby with a major malformation, and
25 our denominator at-risk population there is slightly

1 over 50 pregnancies.

2 Well, the question just came up a little
3 earlier, is about what's the phenotype associated with
4 this exposure? This is the organ systems which are
5 primarily affected. The brain is by far and away the
6 most sensitive organ to the effects of this drug, and
7 hypotonia is one of the most common adverse
8 neurological outcomes that we see from exposure to
9 this drug. Other effects are on the face, and I'll go
10 into detail about that a little more. Congenital
11 heart defects of a very specific nature, this drug has
12 specific effects on certain developmental processes in
13 the developing heart. It does increase the risk for
14 all types of congenital heart defects, it specifically
15 affects the process of aortical pulmonary septation,
16 which is the division of the single heart tube into
17 the pulmonary artery and the aorta. That's the
18 primary development process it seems to affect, and
19 this is most often when these children have fatal
20 birth defects, this is most often the cause,
21 irreparable congenital heart defects.

22 In addition, they have T-cell deficiencies
23 from conthymic hypoplasia, and hypocalcemia frequently
24 from parathyroid deficiency, and that combination of
25 heart defects, thymic deficiency and parathyroid

1 hormone deficiency is known as the DiGeorge anomaly
2 for clinicians who are familiar with that term.

3 This is not the full range of abnormalities
4 that we've seen from Acutane, but this is the most
5 common -- these are the most common organ systems
6 affected. In the most severely affected children,
7 there are a number of other parts of the body that can
8 be affected, but I don't think it's valuable to go
9 into those details this morning.

10 So, this gives you from our prospective
11 cohort, and our listing of some of the abnormalities
12 that these children have, again, organized into brain
13 abnormalities, craniofacial and other, and among the
14 brain abnormalities we see both hydrocephalus and
15 enlarged ventricles in the brain that are where the
16 ventricles are not under pressure, so that's to
17 differentiate that from hydrocephalus. Cranial nerve
18 functions are particularly susceptible to the effects
19 of this drug, optic nerve hypoplasia, torsos and
20 pupillary dysfunction, facial nerve paralysis. The
21 drug seems to have a particular effect on the
22 development of the hind brain, and that results in
23 brain stem abnormalities and cerebellar anomalies, so
24 you get cerebellar hypoplasia here, here, again, more
25 cranial nerve deficits, visual problems and effects on

1 cranial nerves, the motor nuclei, primarily, although
2 we also see pupillary dysfunction as a common adverse
3 effect of this drug.

4 On the facial area, the most common -- I'll
5 actually show these abnormalities in a few minutes, so
6 small jaws, ear malformations, facial asymmetry, those
7 are the common defects.

8 In our prospectively followed group of
9 children, heart defects are much less common than
10 brain and craniofacial ones.

11 I'll just skip that slide, that's just more
12 of the same.

13 The craniofacial phenotype is basically the
14 most common abnormality we see as mild facial
15 asymmetry, followed by external ear malformations,
16 which are much more common than middle ear
17 abnormalities, and those are more common than inner
18 ear malformations. It's rare that we see inner ear
19 malformations, except in the most severely affected
20 children. The ear canals are frequently stenotic and
21 irregular. The mandibular hypoplasia tends to be
22 pretty mild and associated with facial asymmetry.
23 Cleft palate is not a common feature of this
24 embryopathy, I'm only aware of about four cases.
25 These children have abnormal teeth, primarily because

1 we think this drug targets cranial neurocristal cells,
2 and they contribute to all of the tissues of the teeth
3 except the enamel layer, and we have ongoing studies
4 now where we've collected about 100, 150 deciduous
5 teeth from these kids as they've gotten older, and
6 have ongoing studies looking histologically at those
7 teeth. It's a nice way to get a free biopsy of tissue
8 that we think is likely to be affected by these drugs.
9 And, hair patterning abnormalities are quite common
10 among these children as well.

11 I just show some typical slides, and I have
12 to say, because I feel like I didn't make a big
13 impression on this committee in the past, I brought
14 some of the more severely affected children, as
15 opposed to questions that came up earlier about the
16 full range of this phenotype. This is a child who
17 died with congenital hydrocephalus, a severe cardiac
18 defect, no thymus, and you can see here the severe end
19 of the spectrum of effect is complete absence of any
20 development of the external and middle ear. You can't
21 see the middle ear, obviously, here.

22 This is another severe ear malformation, in
23 which, basically, there's only the tragus of the ear
24 and a slit-like canal present, another boy with a
25 severe micrognathia with no canal present. Here's

1 part of the hair patterning abnormalities I mentioned,
2 that includes areas of alopecia that some of these
3 children have.

4 This is a boy whose mother took the drug
5 only in the second trimester of pregnancy, just to
6 give you some idea of the mild end of the spectrum of
7 effects you get from the second trimester, sagittal
8 craniosynostosis, marked epicanthal folds, and mid-
9 facial underdevelopment, very long philtrum, that's
10 the area between the upper lip and the nose. This boy
11 has delayed development, learning disabilities and
12 speech problems as well, so that there is definitely
13 an effect from this drug when it's used in the second
14 trimester. The effects are different and primarily
15 result in mild craniofacial abnormalities such as
16 this, and effects on speech and learning.

17 I'll show some slides of some of the
18 central nervous system effects. This is a child who
19 died with severe hydrocephalus. This is a cross
20 section of the brain showing severely enlarged
21 ventricles and very little cortical brain present.
22 The hydrocephalus can be quite severe, and when
23 combined with a heart defect almost always leads these
24 children to die.

25 This is the characteristic cerebellar

1 malformation. Here you see the brain stem, the two
2 cerebellar hemispheres and the complete absence of any
3 midline cerebellar tissue. This child has a Dandy-
4 Walker malformation, with no absence of the vermis,
5 and I think if you look at the two cerebellar
6 hemispheres you can appreciate a number of asymmetries
7 in the formation of the folia of the cerebellum as
8 well.

9 Another slide showing a Dandy-Walker
10 malformation. This is, again, the brain stem, two
11 cerebellar hemispheres, the cystic dilated roof of the
12 fourth ventricle, the characteristic abnormality of
13 the Dandy-Walker malformation, and these cerebellar
14 abnormalities, both major and minor, are probably what
15 causes these children to have hypotonia.

16 There is a child showing some of the,
17 again, craniofacial features. He's got a widow's
18 peak, which is hard to see, he doesn't have much hair
19 yet, epicanthal folds of hypertelorism, which is not
20 a very common facial feature, but if you look at the
21 size of the pupils this child has both strabismus and
22 asymmetric pupils, a common finding. This boy is
23 confined to a wheel chair, he's blind, deaf, has
24 severe hypotonia and has never walked.

25 This is his CT scan showing the severely

1 hypoplastic cerebellum right here, surrounded by
2 fluid.

3 This is another neurological feature, the
4 facial nerve paresis, which you can see actually it's
5 on this side of the face, when he laughs he doesn't --
6 he's unable to move his eyelid very well, and this has
7 asymmetry of facial expression due to this
8 abnormality.

9 Lastly, just to show you why some of these
10 children have persistent -- some of the children who
11 come out looking normal have learning disabilities and
12 lowered IQs. This is a cross section through a
13 cerebellum of one of the patients who died. This is
14 the edge out here of the foli of the cerebellum, so
15 this is a large honking heterotopia made up all of the
16 cell types of the cerebellum sitting -- lying within
17 the middle of a fol of the cerebellum. So, what we see
18 microscopically in the brains of these children are
19 heterotopic collections of poorly differentiated cells
20 in both the cerebellum and cortical areas, in
21 particular, the hippocampal gyrae is an area where
22 we've seen a lot of these heterotopic nests of poorly
23 developed and undifferentiated cells.

24 Well again, the study we have ongoing,
25 we've looked at all these kids when they were five

1 years old, and are currently looking at them when they
2 are ten. We look at general mental ability, language-
3 based processing, visual, perceptual processing,
4 drawing ability, and, actually, that's a remarkable
5 area where these children, if there's any specific
6 deficit these children have, that's one thing that
7 we've noted, they are terrible drawers and colorers.
8 They have a marked inability to be able to look at a
9 drawing or an object and be able to copy that. It's
10 one of the most consistent deficits in these children
11 that we've noted, and this is true in children who
12 otherwise look like they are unaffected as well.

13 Executive control functions is a major
14 problem for these children as they get older. In the
15 last couple of months, I've had phone calls from two
16 county sheriffs in different parts of the country from
17 these kids who, as they now are becoming teenagers,
18 have such poor executive functions that they'll do
19 ridiculous things like break into a store and then
20 call the police and tell them that they've just done
21 it. So, they have very poor judgment, get themselves
22 into all kinds of trouble, and this falls into a
23 category of control over organization of their life
24 that psychologists refer to as executive control
25 functions.

1 We also assessed articulation, hearing
2 issues and motor coordination, and I'm only going to
3 show one slide of these results. This is our results
4 showing full-scale IQ scores in these children at age
5 five, and this is using the Stanford-Binet IV, and,
6 again, these were administered to study these
7 children, Doctor Adams and I traveled together, so
8 these are observer blinded assessments of IQ done at
9 age five, within three months of their fifth birthday.

10 In green is our control group of kids,
11 again, they are all age matched, so they are all --
12 all of these kids were tested within three months of
13 their fifth birthday. And, for those of you not
14 familiar with IQ scoring, it's normed basically at
15 100, with two standard deviations on either side of
16 the mean score of 100. And, as you can see, our
17 control group clusters right here in the middle range
18 of full-scale IQs, whereas the exposed children have
19 a downward shift, such that about 50 percent of our
20 study population functions with a full-scale IQ of 85
21 or below. And, children who function in that range,
22 most of them will need special education services, and
23 our prediction is that many of the children even
24 functioning in this category will have difficulty
25 living independently as adults, based on the

1 assessments that we've done with them.

2 So, in summary, this is how the picture
3 looks. Of exposed pregnancies, 40 percent of them end
4 in spontaneous abortion. Of the 60 that lead to
5 pregnancies that reached 20 weeks or beyond, there's
6 about a four to five percent risk of perinatal
7 mortality, so in our prospectively followed group of
8 children risk of mortality is quite low.

9 In our retrospectively identified case
10 series, we have a mortality experience approaching 70
11 percent, so that severity of the phenotype in this
12 population versus our retrospectively identified
13 population is quite marked.

14 Again, a doubling of the risk of
15 prematurity, 16 percent, risk of major malformation
16 overall is about 25 percent, but among those who take
17 the drug more than 15 days after conception that risk
18 is about 35 percent, and about half of these children
19 have subnormal full-scale IQ scores at age five, and
20 we're still collecting the data to see what their
21 school performance and neuropsychological testing will
22 show at age ten.

23 So, if you could turn the slides off now,
24 and that's the end of my presentation.

25 We've had very little clinical experience

1 with etretinate. I rarely get phone calls about women
2 with concerns about getting pregnant after they've
3 stopped using the drug. One concern I do have about
4 it, and one issue I think the committee should address
5 today, is who is responsible for following up those
6 women, and who ought to be responsible for providing
7 them services such as determining whether they have
8 detectable levels of these compounds in their blood
9 after they've stopped therapy.

10 In this regard, I think the manufacturer
11 has been quite remiss. The calls I've had from women,
12 they've all been refused the service of having blood
13 levels done by the manufacturer, and I've had to
14 scramble to find researchers who don't normally do
15 diagnostic testing who will do the HPLC assays for
16 these women to tell them whether or not they have
17 detectable levels of this compound in their blood.

18 I think this is a service that ought to be
19 offered by the manufacturer, and I hope this is an
20 issue that the committee will discuss and deliberate
21 on today. Somebody needs to provide this service, and
22 in my opinion it seems like it most logically falls on
23 their shoulders.

24 So, I don't really have much in the way of
25 clinical experience with adverse effects of etretinate

1 to discuss today. The questions that came up earlier
2 about how similar is the phenotype, I think it's quite
3 similar, from the case reports that have been
4 published there are some differences. There have been
5 case reports of etretinate used either before --
6 during pregnancy or women who have gotten pregnant
7 within a reasonable period of time afterward and have
8 had malformed babies, to think that other aspects of
9 this phenotype would include neural tube defects like
10 spina bifida and anencepaphoy, and limb reduction
11 defects, which have been reported with etretinate
12 exposure, those are very uncommon outcomes of exposure
13 to Acutane. I'm only aware of two children who have
14 limb reduction defects associated with Acutane
15 exposure and one with spina bifida.

16 So, I'll stop there and be happy to answer
17 any questions.

18 CHAIRMAN McGUIRE: We have a few minutes
19 for questions for Doctor Lammer. Yes.

20 DOCTOR CANTILENA: Doctor Lammer, just a
21 question in terms of quantitating exposure. It seems
22 like your, you know, yardstick for exposure was in
23 terms of, you know, the timing, either, you know,
24 prior to day 15 or after. Were there any assessments
25 made in terms of, you know, quantitating either how

1 long the individual had been on the therapy or, you
2 know, dose, you know, kinds of information as well?

3 DOCTOR LAMMER: Yes, I didn't put those
4 slides in because of the time limitations. We've
5 looked at the dose response analyses in a number of
6 ways, looking at both setting up doses into quartiles
7 and also using mean dose, and we tend to use the
8 highest dose that the woman was on after conception as
9 our figure, because occasionally there are women whose
10 dose changes while they are pregnant.

11 When we've looked at it with a logistic
12 regression model, where we've modeled the risk over
13 the range -- the recommended therapeutic range of the
14 drug from a half up to two milligrams per kilo per
15 day, we basically find that going from the lowest
16 therapeutic dose to the highest, if we model our data
17 that way, you get about a two-fold increased risk from
18 the lowest dose to the highest, but it's not
19 statistically significant, and that's using dose on a
20 milligram per kilo per day basis.

21 So, if dose is a factor related to the
22 teratogenic effects, it's a small factor.

23 Was there more to your question?

24 DOCTOR CANTILENA: No, but in follow up
25 then, you know, the length of time that the patient

1 was exposed, you know, during the pregnancy, is that
2 also a factor do you think, or is it just, you know,
3 before or after 15 days?

4 DOCTOR LAMMER: The only real important
5 factor we found is more related to timing. The mean
6 number of days during pregnancy that women in our
7 study used the drug is 30 days, and we've looked at
8 that in terms -- if you compare the mean number of
9 days in women who have had babies with major
10 malformations to those who have not, there's no
11 difference. They are both around 30 days.

12 So, the timing seems to be, in our
13 estimation, the most important factor, and it's
14 probably related to the timing of when the embryo
15 fetal circulation gets established. That is probably
16 a requirement in order to get the teratogenic effects.

17 DOCTOR MCKINLEY-GRANT: Have you seen -- I
18 have two questions, actually -- have you seen a
19 decrease in the number of birth defects since the
20 extensive permission and consent form has come about,
21 for Acutane?

22 DOCTOR LAMMER: No, I have not really, but
23 what I have noticed, from beginning just before 1990,
24 is that the cases that I get consulted about are
25 overwhelmingly now women who stopped the drug early in

1 pregnancy. So that, I think situations where women
2 clearly took the drug well into the pregnancy are
3 probably almost universally going for termination of
4 pregnancy and not even calling people like me for
5 advice about the risks.

6 That's more the trend that I've noticed, is
7 that I only get called about the really difficult
8 counseling cases, where women stopped taking the drug
9 right around the 15th day and things like that.

10 To give you an example, I probably get one
11 or two of these calls a month, I would say.

12 DOCTOR MCKINLEY-GRANT: The other point I
13 wanted to note was just your comment about not seeing
14 many women with -- or getting any calls from women who
15 have been on etretinate about pregnancy, and I think
16 that may reflect the fact that this is a drug that is
17 very, very rarely used in women of child-bearing age.

18 I mean, it would be used, I think, in a
19 case of a woman with pustular psoriasis, who it's
20 really life threatening, and which it can be a disease
21 that is life threatening, but I think the use of
22 etretinate in a woman of child-bearing age, for just,
23 you know, plaque-type psoriasis is just not something
24 that would be done, and that the women are probably
25 advised -- I mean, it's a very big decision to decide

1 that you can never have children again, if you are
2 going to be on that medication. So, I think that may
3 be reflected in what you are saying.

4 DOCTOR LAMMER: I agree. None of the women
5 I received calls from had pustular psoriasis, and most
6 of them were unaware of the warning that they should
7 not get pregnant again, not again, but ever. I mean,
8 I'm not a dermatologist qualified to determine whether
9 or not these women should have been on the drug or
10 not, but in questioning them they had run of the mill
11 plaque-like psoriasis, and none of the had the
12 pustular form, nor were they people who were
13 particularly ill like the population that was
14 described to me at this meeting some years ago, who
15 were the candidates for this medication.

16 CHAIRMAN MCGUIRE: Doctor Buntin?

17 DOCTOR BUNTIN: You showed a slide of a
18 child who was exposed during the second trimester. I
19 was wondering if you recall the circumstances for
20 which the medication was prescribed to the mother?

21 DOCTOR LAMMER: Acne. She did not know she
22 was pregnant. I've not ever met a woman who knowingly
23 took this drug, knowing that she was pregnant.

24 I know it sounds hard to believe, but
25 there's lots of people who don't know they are

1 pregnant into their second trimester.

2 CHAIRMAN McGUIRE: Doctor DiGiovanna.

3 DOCTOR DiGIOVANNA: Just to continue on
4 Doctor McKinley-Grant's note about the infrequent
5 nature of teratogenic outcomes associated with
6 etretinate. I believe that initially when etretinate
7 was made available in Europe and in other countries,
8 there was very little concern about teratogenic risk,
9 and there were a number of -- as the concern increased
10 there were a number of reports of women who had taken
11 etretinate during therapy and delivered normal
12 children.

13 I think that there may be some difference
14 in the teratogenic potential of etretinate and
15 Isotretinoen, and maybe we'll hear more about that
16 later, but I think that there is some suggestion that
17 Isotretinoen may be a far more potent teratogen at
18 least in humans, and I think initially there may have
19 been some confusion in that some of the animal studies
20 did not -- had actually reported the reverse that,
21 more suspicion with etretinate.

22 DOCTOR LAMMER: I agree with you. I think
23 there probably is a difference in teratogenic
24 potential on a per milligram basis.

25 CHAIRMAN McGUIRE: Doctor Mindel?

1 DOCTOR MINDEL: Is there any information
2 about the birth rate problems with people that just
3 have psoriasis untreated? Is there any increased risk
4 of spontaneous abortions, malformations?

5 DOCTOR LAMMER: I'm not aware of that, but
6 I can't say I've ever seen any information addressing
7 that question. Likewise, I've had people ask me if
8 there's an increased risk for birth defects in women
9 who have severe acne, and to the best of my knowledge,
10 no. But, I don't think it's something that anybody
11 has really focused on very much in research studies.

12 DOCTOR ORKIN: It's a very interesting
13 point you raise, the difference between the 0.5 and
14 one or two makes very little difference in terms of
15 the incidence of these significant side effects,
16 because there's a tendency upon some authorities in
17 acne to use the lesser levels because of lesser side
18 effects, but I appreciate that point that you raise,
19 that there's apparently less of a significant -- no
20 difference in the significant side effects.

21 DOCTOR LAMMER: Yes, in experimental
22 animals, you can demonstrate a dose response effect in
23 terms of risk for teratogenicity, but the magnitude of
24 difference in doses that they are using to show that
25 is totally different than the difference in the

1 therapeutic range for humans, which is quite narrow.

2 To demonstrate a dose response effect in
3 animals requires at least a ten-fold difference in
4 dose.

5 CHAIRMAN McGUIRE: If there are no further
6 questions, thank you, and we will have a 15-minute
7 break, which puts us back in here at 10:45.

8 (Whereupon, at 10:39 p.m., a recess until
9 10:59 a.m.)

10 CHAIRMAN McGUIRE: Will people be seated,
11 please?

12 We're ready to reconvene the morning
13 meeting, and we'll have a presentation from the
14 sponsor by Doctor Robert Armstrong.

15 DOCTOR ARMSTRONG: Can I have the slides
16 on, please?

17 I'd like to thank the FDA for the
18 opportunity to address the committee, and I appreciate
19 the committee's willingness to provide their
20 experience and their wisdom.

21 As we've already indicated today, this is
22 not a simple issue, and not one which can be easily
23 resolved, even when there is agreement on the data,
24 trying to translate that agreement into good medical
25 practice is the challenge, and we very much look

1 forward to the input from the committee in trying to
2 reach that in collaboration with the Agency.

3 I'd like to give an overview of what the
4 presentation will be today. I'm going to start with a
5 statement of goals and objectives, which I have
6 proposed to set the stage with, in terms of the things
7 that we would like to be able to accomplish in the
8 labeling. I'll give a quick review of some of the
9 pharmacokinetics features that we believe are
10 important, a review of the pregnancy data which are
11 available to us, where acitretin exposure is
12 potentially involved, and then put that together in a
13 recommendation for draft labeling, and put together
14 the rationale for that, and then come back to the
15 objective that we would like to be able to achieve in
16 the course of this presentation.

17 So, to start, we have three goals that we
18 would like to keep in mind. The first is the goal of
19 preventing unnecessary sterilization, and this goes to
20 the point that was made in the beginning by the
21 representative of the patients, the National Psoriasis
22 Foundation, and the fact that the indefinite period
23 that is a part of Tegison labeling has led individuals
24 to take that as a way of dealing with an uncertain
25 period of contraception and the risk associated with

1 that.

2 The second goal is the goal of preventing
3 pregnancy during the period of increased risk to the
4 embryo, and we've seen clear slides from patients who
5 were born -- whose mothers had taken Isotretinoin
6 during pregnancy, and those are clear reasons why this
7 is an important goal.

8 And, we also recognize that to optimize
9 this goal one would tend to increase the duration of
10 a contraceptive period, so as to reduce the
11 possibility of ambiguity or difficulty occurring, so
12 there is a tendency to say, with this goal in mind,
13 that a longer duration would be desirable.

14 The third goal, however, is also an
15 important one in our view, and that is that we would
16 like to prevent a situation where an otherwise
17 undesired abortion would be performed because of a
18 concern about a risk to the fetus, when, in fact, that
19 risk had passed. This is an important additional
20 goal, and a particularly difficult additional goal,
21 because to maximize that goal one would tend to err on
22 the side of reducing the period of contraceptive
23 duration, and trying to balance those two goals with
24 opposite directions as they would influence the
25 recommendation is, indeed, the difficult task that we

1 have asked for your assistance in.

2 Now, we have, as the manufacturer of this
3 drug, an objective that we would hope to be able to
4 achieve in the course of this deliberation, and that
5 is that we could formulate a well-defined, a clearly-
6 defined post-therapy contraceptive period, and our
7 reason for that is a very simple one. We've had a
8 long experience with management of teratogenic risk
9 for this drug, as well as for Isotretinoin, and all of
10 that experience leads us to try to formulate very
11 explicit educational messages that can be used for
12 physicians and for patients, and we think that the
13 clearer the message is, the more effective the
14 educational program can be.

15 So, with those goals and objectives in
16 mind, I'd like to change now and give some discussion
17 about the pharmacokinetics data, and I'd like to start
18 off with what we don't know, because I think that this
19 is, in some ways, of critical importance. And, it is,
20 I think in some ways, the weak link in our ability to
21 use a pharmacokinetics argument to formulate good
22 advice.

23 It is not possible to rigorously determine
24 what the period of increased risk is and when it has
25 passed for two reasons, which are interrelated. The

1 first one is, we don't know what the minimum exposure
2 that is required to increase the risk of malformation
3 is. That has not been determined for this drug, and
4 I would say also, to my knowledge it has not been
5 determined for any other drug with teratogenic
6 potential, including some which are possible
7 therapeutic alternatives to acitretin in the treatment
8 of psoriasis, and I'm thinking, in particular, of
9 methotrexate and hydroxy urea.

10 The second point is that we have an
11 assumption that the threshold exposure, and it's a
12 threshold in terms of the dose, the time, and the time
13 during fetal development, would correlate in some way
14 with blood concentration. Now, that is an important
15 assumption for many of the conversations that we have
16 had today, but it's not one that has been validated
17 with experimental evidence. We believe that it is a
18 reasonable assumption, but it has not been
19 established.

20 Now, the point has already been made that
21 what we are dealing with here is the ethyl ester in
22 the form of etretinate and the free carboxylic acid in
23 the form of acitretin, and that the natural conversion
24 in the body is strongly toward the conversion of
25 etretinate to acitretin. But, this slide makes the

1 point, which is a very important one, that anyone who
2 has had etretinate has been exposed to acitretin, and
3 I'm going to develop that a little bit more on the
4 next slide, where I will share with you our
5 experience, that if you give 50 milligram doses of
6 etretinate and 50 milligram doses of acitretin, you
7 actually get higher values, higher concentrations of
8 acitretin in the patients that are treated with
9 etretinate.

10 Now, this is important to some of the
11 information that I'll be presenting to you shortly,
12 because it means is that a patient who has been
13 treated with Tegison with etretinate is actually
14 exposed to higher concentrations for longer periods of
15 time of acitretin, and this will be important because
16 we propose to increase our ability to look at the
17 actual outcomes of exposed pregnancies, or potentially
18 exposed pregnancies, by combining the experience with
19 both drugs into one presentation. We think that this
20 is justified because those individuals who were
21 treated with etretinate actually have a longer and
22 greater exposure, so we believe that this is a
23 conservative construction in terms of estimating risk.

24 I'll also talk a little bit about the
25 ethanol interaction with acitretin to form etretinate,

1 and we've already talked about the half life of the
2 two drugs and don't need to dwell on that further.

3 I'll go back now for a moment to this
4 clinical pharmacology study involving volunteer
5 subjects who took a 100-milligram dose of acitretin.
6 Now, you should appreciate that the highest
7 recommended dose for starting a patient on acitretin
8 will be 50 milligrams, so this represents about double
9 the maximum recommended dose. And, it also uses a
10 very large dose of alcohol. This represents
11 approximately one pint of Vodka taken over the study
12 period, and I can tell you that every one of the
13 subjects who participated in this met the legal
14 definition of intoxication, as well as experienced
15 nausea and vomiting, so this is a condition which we
16 believe represents a very -- a set of conditions that
17 should favor this reaction occurring.

18 And, I'd like to present the data here on
19 these subjects, and what we have grafted with the blue
20 line is the concentration of etretinate at varying
21 time points up to 24 hours, and I would say that the
22 drug is not detectable at 48 hours. So, this is the
23 time when it can be found, and it was found in all of
24 the individuals when they took both the acitretin and
25 the alcohol.

1 What we don't have is any detectable
2 levels, and here's the limit of detection at five
3 nanograms per mil, in those individuals when they took
4 the acitretin without alcohol in a single time point.

5 Now, the conclusions of that are that
6 plasma concentrations of etretinate were not detected
7 when acitretin was taken without ethanol. The peak
8 mean etretinate concentration in plasma was 55
9 nanograms per mil, and that occurred at six hours when
10 the acitretin was taken with ethanol. And, the area
11 under the curve of that etretinate that was formed was
12 approximately comparable to what a five milligram dose
13 of etretinate would do. I think that's an important
14 point, because what that illustrates is that you have
15 a much lower exposure to etretinate when it is formed
16 in conjunction with this very high alcohol burden
17 optimized, if you will, to provide conditions under
18 which etretinate could form. So, we are expecting
19 that this would actually represent a much better, much
20 lower exposure to etretinate than would be seen in
21 patients treated with Tegison.

22 Now, with that as a review of the
23 pharmacokinetics data, I'd like to review for you our
24 experience with pregnancy and the outcomes of
25 pregnancies that have been reported.

1 And, as Doctor O'Connell has already
2 indicated, there is a concern about the risk of bias
3 of ascertainment in including retrospectively
4 ascertained cases, so what I'm going to concentrate on
5 today are those prospectively ascertained pregnancies.

6 There are two aspects which we believe are
7 useful in considering the question of what effect did
8 prior treatment with the drug have on -- if any -- on
9 the pregnancy, and the first of those conditions is,
10 has there been an increase in the incidence of
11 malformations? Is it higher than the spontaneous rate
12 of major malformations, which has been estimated in
13 the three to five percent of pregnancies through the
14 general experience where there is no treatment with a
15 retinoid or other teratogenic agent.

16 The second possibility is that even if the
17 actual incidence of malformations is not increased,
18 there's still the possibility that a specific pattern
19 might occur, and that that pattern would have a much
20 higher relative risk than would be expected by the
21 coincidence of independent events leading to a
22 conclusion that there was an association with the
23 drug. So, we are going to look at both aspects of
24 this approach.

25 Now, to do this, I'd like to go through a

1 little bit of what happened to the case reports that
2 came to us, as we come down to this analysis for your
3 clarity. The first point is that we've had a total of
4 438 cases reported to the company since either of
5 these drugs was being used in human trials, and out of
6 that 188 of the cases were reported to us
7 retrospectively, so if we remove them from a
8 consideration for the estimate of incidence, that
9 leaves us 250 cases to consider.

10 Out of these cases, 25 were lost to follow
11 up and we have no information on them, so that takes
12 us down to 225 cases to consider. Nine of the
13 pregnancies were still continuing at the time the data
14 were pulled together, so we don't know if there is an
15 outcome from those yet, so we'll have to look at those
16 later. That leaves us 216 cases to consider. The
17 discrepancy which we detected was that we had three
18 individuals who had been treated initially at some
19 time in the past with etretinate, and subsequently
20 treated with acitretin, and when we broke out our
21 tables, presented those patients who had been treated
22 with acitretin they appeared in those tables, and when
23 we put the tables where we looked at patients who had
24 been treated with etretinate they appeared in those
25 tables. When we put them back together again to do a

1 calculation of relative risk, we actually needed to
2 take the duplicate recording of those out, and I'll
3 show you in a moment where that comes out. But, in
4 any event, taking those three cases out leaves us with
5 213 cases. And finally, an important point, 93 of
6 these pregnancies were terminated without any
7 information about the fetus, so that leaves us with
8 120 cases where we actually know something about what
9 happened to the fetus and are able to then use that to
10 calculate incidence figures.

11 So, I'd like to show you what the raw data
12 look like from these 120 cases. What we have are
13 really three categories of outcome. One would be the
14 birth defect outcome. This is any malformation that
15 was reported, according to the ICD-10 classification.
16 The second group would be other disorders that were
17 reported, and this might be prematurity, or it might
18 be hyperbilirubinemia, et cetera. And then finally,
19 we have those outcomes where the child was normal, and
20 there was no evidence of any effect.

21 And then, what we have is, when the
22 pregnancy occurred, in relationship to therapy, so the
23 first column is those pregnancies that occurred during
24 treatment. And then, we have six-month periods up to
25 two years provided for you, so there are four periods

1 there, a group of pregnancies prospectively
2 ascertained that occurred more than 24 months after
3 the drug had been stopped, and three cases where we
4 actually don't know exactly what the relationship was,
5 haven't been able to indicate that. All of those
6 three cases, however, turned out to have been normal,
7 so that simplifies the calculation a bit, and that
8 gives us the total of 120.

9 Now, what we can do to build on this is to
10 say, if you look at the outcome of birth defect,
11 relative to the total number of individuals in each of
12 these groups, we can calculate a percentage incidence.
13 And, what we will show you in the next slide is what
14 those percentage incidents look like for the group
15 where the pregnancy occurred during therapy for each
16 of the first four or six-month periods, and then a
17 combined table that shows all of the patients -- all
18 of the outcomes within the first 24 months, and this
19 is what the data then would look like.

20 We have a 25 percent incidence of birth
21 defects for those pregnancies that occurred during
22 treatment, and during the two-year period immediately
23 following treatment the incidence of birth defects is
24 actually five percent.

25 If we break that 24-month period into four

1 sub-intervals, what you can see are, respectively, a
2 seven percent incidence in the zero to six-month
3 period, no abnormalities of birth defect abnormalities
4 in the six to 12-month interval, ten percent in the 12
5 to 18-month interval, and six percent in the 18 to 24-
6 month interval.

7 Now, one of the things that concerns us
8 about this is that there is, in fact, if you look over
9 the entire two-year period immediately following the
10 cessation of therapy, there is an incidence of five
11 percent which is right at what the spontaneous
12 reported occurrence rate would be.

13 If you postulate that there should be a
14 higher probability of getting an effect at the time
15 when the drug is higher, and if you take the position
16 that the drug should be eliminated progressively over
17 time, you would expect to see the highest incidence in
18 the period closest to the time the drug was
19 discontinued and a progressive fall off to the
20 baseline level or the spontaneous rate as you got away
21 from the influence of the drug.

22 And, in fact, what the data show is that we
23 have an, essentially, flat curve here that does not
24 show a heightened incidence in the immediate period
25 with a progressive fall off.

1 Now, one of the difficulties that is
2 presented by this kind of an analysis is that we have
3 a relatively small number of cases. The total number
4 of cases in this two-year period is 94, and that is
5 not enough to give you stable estimates when you
6 divide that into cells that vary in size from 16
7 individuals up to 29 individuals. Nevertheless, we do
8 think it gives you an idea of what the experience has
9 been, and what the relationship between the incidence
10 of malformations is as it relates to drug.

11 Now, the second thing that we talked about
12 was the possibility of there being a specific pattern,
13 and this retinoid embryopathy is based, as Doctor
14 Lammer has reviewed for us, on cases exposed to
15 another drug in the class, Isotretinoin, and I'm not
16 going to go through these again, other than to say
17 that craniofacial, cardiovascular, thymus and
18 sometimes parathyroid and central nervous system are
19 the organ systems that are most commonly involved in
20 these malformations.

21 This table presents for you all eight of
22 the cases where a malformation was reported, and the
23 final one that's listed here is the instance of a
24 duplicate, because the patient had actually been
25 treated both with acitretin and etretinate, and it is

1 this case here under acitretin that we have left in
2 the analysis, and the case down here where the same
3 pregnancy occurred but at a longer period of time
4 after treatment with etretinate.

5 What you can see is that among those
6 outcomes where there was a malformation, it was only
7 those that occur -- where the pregnancy occurred
8 during treatment that have a feature common to the
9 retinoid embryopathy that was outlined on the
10 previous slide.

11 In contrast, where the pregnancy occurred
12 at varying time periods after the drug had been
13 discontinued, the malformations that we saw were a
14 congenital hernia, a club foot, an undescended
15 testicle, a gastrointestinal abnormality, and a
16 congenital absence of one hand and wrist, which might
17 represent a strangulation from an amniotic band or
18 possibly some other cause, but not the typical kind of
19 abnormality that's been associated with retinoid
20 exposure.

21 Now, that brings us to the crux of the
22 discussion for today, and that is, how do we put this
23 information together to come to a recommendation for
24 a post-therapy contraceptive period.

25 The first set of data that I would like to

1 review for you is really pharmacokinetics data, and
2 I'd like to emphasize here that this is all subject to
3 the significant limitation that we can calculate with
4 much greater comfort how much of the drug that was
5 available was eliminated. We can calculate with
6 somewhat less comfort what the actual exposure might
7 have been to the drug over time, but what we don't
8 have any clear guidance on is how much drug do you
9 have to eliminate before you have gone below the
10 threshold where an increased risk occurs.

11 So, the first point is that if you have
12 acitretin without etretinate, most of the drug would
13 be eliminated within a two-month period, because the
14 half life of the drug is two days. We do know that
15 concurrent ethanol and acitretin can have an
16 interaction to form etretinate, and that demonstrated
17 mechanism then gives patients the option to avoid
18 ethanol entirely, but if they do not avoid ethanol
19 entirely the amount of etretinate that they are
20 exposed to is still very much less than it would have
21 been had they been treated with etretinate itself.

22 And then the question of how much
23 etretinate that was formed would be eliminated after
24 varying time periods has been reviewed already and
25 calculated, that it's two years with a 120-day half

1 life as the mean, or three years if you take the most
2 extreme half life and use that. But, the difficulty
3 here is that we know that the exposure to the burden
4 of, if you will, etretinate is much lower in the
5 patients who have been treated only with acitretin.
6 And, therefore, we don't really know that these
7 periods can be compared against how low the drug has
8 to be before the risk is avoided.

9 The second point has to do with the
10 experience with pregnancies, and we can say, based on
11 the information that we have, that pregnancies have
12 occurred where the patient had taken acitretin or
13 etretinate is limited, but it does not indicate an
14 increased risk of malformations occurring, of any
15 malformations incidentally, this is not restricted to
16 those that have been associated with retinoid
17 exposures, but any malformations. Not only is that
18 true two years after treatment, but it's also true for
19 the two-year period immediately following therapy.

20 So, that leaves us with our objective that
21 we would like to be able to achieve today, and that
22 would be to come to a clear-cut educational message
23 that we could use to try and focus physicians and
24 patients on the kinds of steps that they could take
25 to avoid any of the undesired outcomes and to achieve

1 the three goals that were outlined for you on the
2 second slide. That's really all that I planned to say,
3 but I would be happy to answer questions if there are
4 any.

5 CHAIRMAN McGUIRE: Let's start with
6 questions for Doctor Armstrong. Yes.

7 DOCTOR MCKINLEY-GRANT: In, let's see,
8 which slide was it, my question was in the length of
9 time that the acitretin was present, was there any
10 indication that weight of these patients were -- you
11 know, I know with etretinate we tend to -- it lingers
12 in obese patients, has there been any work done with
13 acitretin, in terms of the levels, plasma levels?

14 DOCTOR ARMSTRONG: I think the important
15 distinction here is that etretinate has a high
16 affinity for fat, because it is not a charged
17 molecule, and because it has that high affinity for
18 fat it does get stored in fat for a longer period of
19 time, and that is the reason, we believe, that drug
20 can be found in the plasma much longer than it would
21 be expected to without that kind of adipo effect.
22 Because acitretin has a free carboxylic acid, it is
23 charged, it doesn't have that affinity for adipose
24 tissue, and we believe that's why the half life is
25 shorter, and that's why we think that the patient's

1 body weight is not as important in this instance as it
2 is in the cases with Tegison.

3 CHAIRMAN McGUIRE: Doctor Lammer?

4 DOCTOR LAMMER: That was a really nice
5 presentation.

6 DOCTOR ARMSTRONG: Thank you.

7 DOCTOR LAMMER: I have a couple of comments
8 and kind of combined questions. A lot of the
9 conclusion about whether there's an excess number of
10 adverse outcomes of pregnancy in the cohort that you
11 followed is dependent on a historical comparison
12 group, in terms of the expected number of birth
13 defects.

14 I've worked in two birth defects registries
15 at the CDC and for the California Birth Defects
16 Registry, and the expected number of birth defects you
17 see in a cohort population you are studying is
18 dependent on two things, the range of defects you
19 choose to count and the length of time after birth
20 that follow up occurs.

21 So, your choosing to using a five percent
22 figure, or three to five percent, in most registries
23 that would be a high number.

24 Most birth defects registries in this
25 country would use a figure of two to three percent for

1 the expected rate of birth defects ascertained between
2 birth and one year after birth, and to really use an
3 expected number you need to clearly define what the
4 range of outcomes is that you are counting and how
5 long your follow up is, in order to have a comparison
6 group from which to draw an expected frequency.

7 I don't envy your problem. I think it's
8 difficult to know for this type of a study exactly
9 what the expected should be for a population not
10 exposed to the drug, based on the way that follow up
11 is done in this kind of a study.

12 CHAIRMAN McGUIRE: Doctor Cantilena.

13 DOCTOR CANTILENA: Yes, I have, actually,
14 I think, several pharmacokinetics questions. I think
15 sort of one of the keys that I'm struggling with is
16 that you really are trying to figure out, in terms of
17 translating to risk, what the overall graph is going
18 to look like of the steady state accumulation over the
19 course of therapy of the toxic metabolite.

20 And so, I guess one question is, when you
21 look at the figure, the PK figure that you had, slide
22 ten, it appears to me that there's really a
23 significant sort of sustained production of the
24 compound after a single dose. And, I was just
25 wondering if you've characterized the production or

1 the appearance of, you know, the etretinate over time
2 after, you know, single dose, or if you have any
3 information from, you know, a multiple dose situation.

4 DOCTOR ARMSTRONG: Well, what I can tell
5 you is that the data that you see plotted here are all
6 the data that I'm aware of being available. This
7 study was done as part of a process of trying to
8 eliminate a number of different possibilities that we
9 considered to explain how etretinate might appear in
10 the blood of people who had only been treated with
11 acitretin, and the formation of the ethyl ester,
12 because of a drug interaction with ethanol, ethyl
13 alcohol, if you will, was one of the theories that we
14 tested.

15 So, we designed the trial that we intended
16 to optimize the possibility, if that interaction
17 occurred --

18 DOCTOR CANTILENA: Sure.

19 DOCTOR ARMSTRONG: -- to be shown.

20 DOCTOR CANTILENA: I understood that, but,
21 I mean, here you are showing average data. I guess
22 part of the question is how much variability was there
23 across these subjects. And, really, the essence of
24 the question is, what you are trying to define, or
25 what I'm trying to visualize, is really what is going

1 to be the dose input rate for the etretinate on, you
2 know, patients who are involved in that, you know,
3 therapy who use ethanol or, perhaps, another substance
4 in the diet that we haven't explored yet that can
5 facilitate the conversion.

6 And, I guess the whole essence of this
7 argument is that, is it two years, is it three years,
8 is it at least three years, whatever this comes down
9 to for me in my mind is, well, what is the time course
10 of exposure? And, the time course of exposure has to
11 come from, well, you know, what is the dose input
12 rate. So, I guess has your pharmacokinetics section
13 come up with a model, if you will, you know, based on
14 this, and also, the current assay sensitivity is a lot
15 lower than this figure now, right?

16 DOCTOR ARMSTRONG: The assay -- this assay
17 has a quantification limit of five nanograms per mil,
18 but it has a detection limit that's lower than that.
19 The detection limit is down about a tenth of a
20 nanogram per mil.

21 DOCTOR CANTILENA: Okay, so that's actually
22 a fairly huge step off in terms of -- so, you can
23 probably increase the sensitivity or lower the limit
24 of quantification with some improvements then.

25 DOCTOR ARMSTRONG: I'm not sure that we can

1 lower the limit of quantification, because we can
2 detect it, and I think the concern that I have about
3 that approach is that the relevance of those low
4 numbers really depends on how sensitive your assay is,
5 and you could always argue that if you had an assay
6 sensitivity improved by an order of magnitude, or two
7 orders of magnitude, or three orders of magnitude, you
8 would end up with being able to detect a drug for
9 progressively longer periods of time. The question
10 is, how low is low enough, and that's the question for
11 which we don't have an answer.

12 DOCTOR CANTILENA: Exactly.

13 DOCTOR ARMSTRONG: And, which is, I think,
14 the critical one to being able to use a
15 pharmacokinetics argument, or even a direct assay of
16 levels in a patient's blood, to determine what the
17 risk is.

18 DOCTOR CANTILENA: Right, but I think the
19 point of my question was that if you improved your
20 assay you would probably increase your confidence in
21 the pharmacokinetics for the production of the
22 metabolite, and that increased confidence could then
23 improve your model input to really generate, you know,
24 through simulations, you know, what the exposure would
25 be. And also, another point is, this is a single dose

1 exposure, so it's really not relevant to the chronic
2 exposure, the intermittent use of ethanol or other
3 substances.

4 So, if you ran those curves now, and I'll
5 ask you if your company has or if the FDA has run
6 simulations, I think that, you know, the picture would
7 be, you know, significantly different as opposed to
8 the single dose.

9 And also, I think if you increased the
10 sensitivity of the assay, or you dropped the limit of
11 quantification, the confidence in the pharmacokinetics
12 parameters used, you know, for that simulation, I
13 think, you know, would go up.

14 And, I think it is relevant, because the
15 other side of the coin of, well, you know, we don't
16 know the threshold, is just that, how, you know, low
17 is safe? And so, I think that's sort of a two-edged
18 sword.

19 But, I guess I would be -- or, I am
20 somewhat concerned at us trying to make a projection
21 out for, is it two, is it three, is it at least three,
22 really based on this, you know, single dose curve
23 without variability when we are trying to sort of
24 generalize into the real-life multiple dose, and it
25 would help me to see a simulation.

1 So, have you got the simulation or has the
2 FDA done the simulation?

3 DOCTOR ARMSTRONG: What you see are the
4 entire data.

5 DOCTOR CANTILENA: Okay.

6 DOCTOR ARMSTRONG: It's plotted as mean
7 data, and we could get the individual patient data.

8 My concern about that is that, we have a
9 number that estimates about a five percent
10 equivalence, area under the curve equivalence of about
11 a five milligram etretinate tablet. By increasing the
12 precision, or the number of individuals studied, or
13 the sensitivity of the assay, what I'm not clear on is
14 how much you are going to change that estimate. Would
15 you expect to change it by doubling it, or halving it,
16 or tripling it?

17 DOCTOR CANTILENA: Well, I mean, I think
18 that, you know, that's an average number, first of
19 all. You know, number two, you only studied one dose,
20 we don't know really what the conversion would be at
21 other doses.

22 DOCTOR ARMSTRONG: Right.

23 DOCTOR CANTILENA: We don't know what the
24 conversion would be over a period of time.

25 DOCTOR ARMSTRONG: Agree.

1 DOCTOR CANTILENA: So, I can't answer your
2 question.

3 DOCTOR ARMSTRONG: And, I can't answer it
4 either.

5 DOCTOR CANTILENA: Well, I think you can,
6 I think if you did the study you would know the
7 answer, and then you'd have the, you know,
8 pharmacokinetics that would help you draw the curve
9 over time. If someone is on this for one year, what
10 does it look like?

11 DOCTOR ARMSTRONG: Well, let me ask a
12 little different approach to this, if I could. We set
13 conditions for this experiment to optimize the
14 possibility of an interaction being demonstrated, so
15 we used a higher than therapeutic dose, and we used,
16 as I said, a large dose of alcohol in a short period
17 of time, producing, not only clinical intoxication,
18 but also nausea and vomiting to go with it. So, this
19 is an extreme case.

20 And, under the conditions set to optimize
21 the potential to detect etretinate, what we got was
22 the equivalent of a five milligram tablet or dose of
23 etretinate.

24 Now, I don't know a relationship, because
25 we have no data on, if you varied either the amount of

1 acitretin given or the amount of alcohol given, how
2 much, if any, you would change the area under the
3 curve, I don't know that, but my assumption would be,
4 and I think it would be a reasonable assumption, that
5 under either of those conditions you would not
6 increase the amount of etretinate produced, you would
7 be more likely to decrease it by reducing either the
8 alcohol or reducing the acitretin.

9 DOCTOR CANTILENA: Well, I guess I would
10 buy the part with the acitretin, simply from a mass
11 balance standpoint, but I'm not sure that you can say
12 that with the alcohol, and, again, I think that is
13 something that can be, you know, tested and proven.
14 It's not impossible. It's a clinical study that can
15 easily be done to answer the question, what is the
16 threshold amount of ethanol? What is, you know, the
17 molar ratio of the substance? What is the time course
18 for the production of, you know, the etretinate? And,
19 is it going to be a factor at therapeutic doses? But,
20 I would want to know, is it going to be relevant at
21 steady state, ongoing, you know, repeat exposure,
22 because I think -- I sense your uncertainty in terms
23 of extrapolating to the steady state situation, and I
24 share that with you, because, you know, we don't have
25 the data, but I don't think these studies are

1 impossible to do, and I think that it would certainly
2 increase our knowledge base and, therefore, confidence
3 in our ability to project to quote actual clinical
4 use.

5 DOCTOR ARMSTRONG: I think there are a
6 couple of points that could be still be made on this.
7 One of them is that we have, in a sense, a therapeutic
8 experience in which we monitored individuals at a time
9 when we did not know that there was an ethanol
10 interaction and actually detected etretinate in the
11 blood of people being treated with acitretin, and that
12 information was presented earlier by Doctor O'Connell,
13 and that ended up being about 16 percent of the people
14 that were followed.

15 The converse of that is that without any
16 directive as to alcohol consumption, 83 percent or so
17 of individuals did not show any detectable etretinate
18 under conditions of taking the drug for a therapeutic
19 indication, without any avoidance of or admonition to
20 avoid alcohol.

21 So, that suggests to me that it can occur
22 under the of typical therapeutic situations in normal
23 living. It occurs at a much lower level than it would
24 in patients who were given etretinate, and that the
25 action step that you would recommend, based on having

1 that kind of a more precise titration would, I think,
2 be the same, and that is, while you are taking this
3 drug, and until you've had a chance to eliminate it,
4 it is advisable not to consume ethanol.

5 And, that's a direction which we have
6 already proposed be included in the labeling for the
7 drug, so it seems to me that whether we might change
8 the values by a certain amount up or down from that,
9 the action item is the same, and we've already taken
10 that.

11 DOCTOR CANTILENA: Well, I guess I would
12 slightly disagree, in that this all comes down to
13 timing. The timing is, how long should the interval
14 be, you know, two, three, or more than three, or at
15 least three, and timing is really based, in my mind,
16 on the kinetics. And, I'm having a hard time jumping
17 from the single dose, what you have here, even, you
18 know, bolstered by the argument. Those were, you
19 know, sort of random samples, who knows how they were
20 done really, and I think that they are not -- you
21 could use that data to see where those folks would
22 fall on the model that you generate from and improve
23 the prospective controlled, you know, PD study.

24 But, for me, it all comes down to timing,
25 and pharmacokinetics is one tool that you can use to

1 answer the time interval, and I guess that's sort of
2 where we, you know, disagree.

3 DOCTOR ARMSTRONG: Well, I don't think
4 we've disagreed on that. In fact, I think that we've
5 agreed that pharmacokinetics can be useful. In this
6 situation, we are faced with, we don't know what the
7 endpoint is, so that clearly limits the usefulness of
8 saying how much the drug will decrease, because you
9 don't know how far you have to have it decrease before
10 your risk is over.

11 DOCTOR CANTILENA: Right, but the other
12 side of the coin is that, in your 20th slide you say,
13 after three years at "extreme" half life of 168 days,
14 well, how do we know that's really extreme in the
15 steady state values. And, you haven't shown us the
16 variability in slide ten, how variable is this
17 population, even in a controlled setting?

18 So, I guess in the absence of data, my, you
19 know, bias would be to be more conservative, and then
20 really when we fill in the data we can then, you know,
21 reassess it, have another look at it, and, perhaps,
22 lower, you know, the time interval. But, I think it's
23 not like we are asking you to go out and come up with
24 the number of molecules needed as the threshold. I
25 mean, I think that's, you know, mission impossible.

1 But, I think from my perspective, what I
2 would ask for would be to enhance the database from a
3 kinetic standpoint, so that we could then be less
4 conservative in the projections, because, really, this
5 is a projection from single dose information to
6 chronic steady state, and I guess that's just really
7 more philosophy than anything else.

8 CHAIRMAN MCGUIRE: Let's have a question
9 from Doctor Guinee.

10 DOCTOR GUINEE: On another topic, in your
11 prospective data, you said that the only people to
12 have a characteristic defect were those who had taken
13 the drug at the time of pregnancy.

14 DOCTOR ARMSTRONG: Correct.

15 DOCTOR GUINEE: In your retrospective data,
16 did the same hold true?

17 DOCTOR MARADIT: Yes, it was the same, that
18 we split the data retrospective reports into different
19 time intervals, and looked at the proportion of birth
20 defects which were today type findings, the proportion
21 of birth defects -- were more -- occupied a higher
22 percentage of birth defects during treatment compared
23 to intervals before conception.

24 So, as we go away, which means that if the
25 interval is -- the timing from the time of conception

1 is long away from conception, then we have a list of
2 nons which we list in our retrospective report.
3 Actually, we have a slide for that, we can show the
4 slide.

5 DOCTOR ARMSTRONG: Now, the actual verbatim
6 terms that were used are supplied in the information
7 that we provided to the Agency to be shared with you
8 as preparation for this meeting.

9 CHAIRMAN MCGUIRE: Do you have other
10 comments, Doctor Guinee?

11 DOCTOR GUINEE: No, thank you.

12 CHAIRMAN MCGUIRE: Okay. Doctor
13 DiGiovanna.

14 DOCTOR DiGIOVANNA: I share Doctor
15 Cantilena's tremendous interest in exactly what
16 happens with the pharmacokinetics in this issue, but,
17 perhaps, another way of extracting some comforting --
18 potentially comforting information with respect to the
19 lowest amount of either of these particular retinoids,
20 which present a realistic hazard might be to look at
21 some other information.

22 I am very comfortable, and I think probably
23 most people here would be comfortable, assessing that
24 etretinate as a drug probably poses a greater risk of
25 long-term retention than acitretin as a drug being

1 converted into etretinate.

2 And, correct me if I'm wrong, but it's my
3 understanding that etretinate is available as a drug
4 in many countries with the indication that
5 contraception be postponed for a two-year period of
6 time, as opposed to in the U.S., where it is
7 indefinite.

8 Is there any data on pregnancies post-
9 etretinate in other countries that would give us a
10 sense that this is, even with etretinate used as a
11 drug which would lead to a larger body store, we would
12 guess, that with the recommendation of only two years
13 that there's data looking at pregnancies past that
14 period.

15 DOCTOR ARMSTRONG: John, I appreciate that
16 point. Paul, could you give us slide 14, please?
17 You've seen the slide, so it's not -- the next slide.
18 This table is both etretinate and acitretin-treated
19 patients. Actually, there are 62 percent of these
20 patients are patients treated with Tegison, Tegison,
21 okay, with the much higher exposure, the much higher
22 fat storage, and the longer duration of exposure, so
23 62 percent of these cases were treated with Tegison
24 only, or Tegison and acitretin.

25 One of the points that I'd like to make is

1 on the next slide. Here at the period where I think
2 we can all agree there is a difference in incidence
3 that we don't think is a coincidental one, the 25
4 percent incidence of malformations in those
5 pregnancies that occur during therapy, is an
6 indication of the teratogenicity of this drug in
7 humans.

8 If we then look out here, the incidence
9 goes down to five percent, and I would submit to you
10 that if you look at the third goal of not having the
11 fear of malformations lead to a therapeutic or induced
12 abortion is a very clear difference. Here, the
13 probability of severe malformation is 25 percent, but
14 if the patient elects to terminate a pregnancy that
15 she would otherwise bring to term, that's 100 percent.
16 And, I think that it's important to make sure that
17 both of those considerations are balanced in the
18 formation of a recommendation.

19 DOCTOR DiGIOVANNA: I'm not sure that
20 answers my question. This is U.S. data?

21 DOCTOR ARMSTRONG: This is worldwide data.

22 DOCTOR DiGIOVANNA: This is worldwide data.

23 Thank you.

24 CHAIRMAN McGUIRE: Doctor Orkin.

25 DOCTOR ORKIN: You may have already

1 addressed this, but just for clarification, one of the
2 things I think that is concern to me and, perhaps, to
3 us, is the fact that there's no verification,
4 certainly, of alcohol intake, and that the individuals
5 may have an ongoing, perhaps, further intake in that
6 16 percent, that may be keep up the subcutaneous store
7 and may go on for considerably longer than the three
8 years, and particularly since we don't know the titer
9 that may still persist as a problem. Could you
10 address that?

11 DOCTOR ARMSTRONG: Yes. The first thing I
12 would say is that that experience was at a time when
13 we were not aware, no one was aware, that there was an
14 ethanol interaction that would lead to the formation
15 of etretinate. So, that experience is without any
16 admonition or advice around avoiding ethanol, so the
17 question of, is the patient giving you an accurate
18 history of her alcohol intake really wasn't relevant,
19 because the patient had not been advised that it was
20 desirable to avoid alcohol.

21 DOCTOR DiGIOVANNA: But, even with the
22 advice we don't know whether the individual is still
23 going to be furtively taking it, and, therefore, the
24 stores may persist, since we don't know the titer.

25 DOCTOR ARMSTRONG: That's correct.

1 DOCTOR DiGIOVANNA: That gives us less
2 security in even the three years, would you agree?

3 DOCTOR ARMSTRONG: I would agree that we
4 don't know that an individual may not give us a
5 different history than her practice, but we also, when
6 we say "at least three years," have made a presumption
7 in the recommendation that does not give any
8 acknowledgement to the fact that the patient who knows
9 that there may be an ethanol interaction may elect to
10 avoid ethanol and, therefore, avoid the one condition
11 where we know there can be a formation of etretinate.

12 So, in a sense, when we take a series of
13 worst case scenarios, the patient knows that there's
14 an ethanol interaction but will drink anyhow, and will
15 drink substantially enough to produce detectable
16 levels, and that she will take, not the mean, but the
17 most extreme half life against an endpoint, a
18 threshold for increasing the risk that is unknown,
19 where, in fact, the actual experience with what the
20 outcome of pregnancies is, and this is the actual
21 experience. I mean, this is not a theoretical set of
22 calculations, these are all cases that have been
23 reported to us where we were able to detect the
24 pregnancy before the outcome was known.

25 So, when you put all those together, my

1 concern is, number one, that we not make a pregnancy,
2 a contraceptive, post-therapy contraceptive period,
3 unduly long, but also that we provide clear guidance
4 so that we can have an effective educational message.

5 CHAIRMAN McGUIRE: Doctor Mindel.

6 DOCTOR MINDEL: I've done a hasty
7 calculation based on a molecular weight of 340, and if
8 your detection is 0.1 nanograms per ml, that would be
9 a blood level of about 10^{-8} , 10^{09} molar. My question
10 is, why discard, as, you know, we'll just keep
11 detecting the drug, why discard a technique that you
12 would want to have at least a lower level than can be
13 detected circulating, at least I would think I would
14 want a toxin at lower than 10^{-9} level, why not make
15 that a criterion that it not be detectable by your
16 assay method as a least requirement for becoming
17 pregnant?

18 DOCTOR ARMSTRONG: I think the difficulty
19 in that approach is that I have no basis for assuming
20 that what the current level is not already well below
21 the threshold for risk.

22 DOCTOR MINDEL: What I'm saying is that,
23 have a criteria that, say, a woman would have to have
24 two assays non-detectable a month apart as a minimum
25 requirement before pregnancy could be considered.

1 DOCTOR ARMSTRONG: I'm sorry, I didn't
2 understand your point.

3 DOCTOR MINDEL: Saying that you would want,
4 by that you would be saying you would want a level
5 lower than 10^{-9} molar circulating.

6 DOCTOR ARMSTRONG: Okay. There are two
7 aspects of that.

8 DOCTOR MINDEL: That are non-detectable.

9 DOCTOR ARMSTRONG: There are two aspects of
10 that, if I understand you correctly. One is, should
11 you look for a non-detectable assay result, and the
12 limitation on that is as I said before, a concern that
13 we don't know that we are not already below the
14 threshold with the current assay sensitivity. And, I
15 don't know what the threshold is, nobody does, nobody
16 does for this drug, nobody does for any other drug,
17 but whatever that level is, we may already be well
18 below that level with the current assay sensitivity.

19 It may be useful to think of an analogy
20 here, because there is another drug that is used for
21 treating this patient population, methotrexate, that
22 is not only known to be a teratogen, but also has
23 other effects on pregnancy, as well as on male
24 reproductivity, and that is that there there is no --
25 you must avoid for at least -- the recommendation is

1 that you should avoid it for one menstrual cycle in
2 women and for three months in men, if my memory serves
3 me. But, it's not something that goes out
4 indefinitely and for prolonged periods of time.

5 DOCTOR MINDEL: That seems to be mixing
6 their reasons for that, but still, I'm getting back to
7 this, the 10^{-8} , 10^{-9} , is not -- for prolonged exposure
8 that pharmacologically is not a negligible level, and
9 I want to get back to that. I'm not going to let go
10 on that, as far as criteria for determining when
11 pregnancy would be allowable. I'm not saying that a
12 10^{-9} level or below it is safe, but are you going to
13 tolerate or going to accept people having that level
14 getting pregnant?

15 CHAIRMAN MCGUIRE: Can we move?

16 Ms. Cohen.

17 MS. COHEN: I'm very curious, in
18 determining how many people actually were part of the
19 program, and some of it you list in Europe, were the
20 criteria in Europe the same in each country? And, I'm
21 looking at all the numbers you have here, how many
22 people did you actually follow through, and what about
23 Europe? I don't quite understand, and what about the
24 demographics and the educational level of these
25 people?

1 DOCTOR ARMSTRONG: Okay. The nature of the
2 information that's reported to us does not give us
3 that kind of demographics that we know what the
4 educational level of these individuals is. The
5 recommendations in Europe have been consistent from
6 country to country. For Tegison, it has been a two-
7 year, post-therapy contraceptive period, for acitretin
8 the initial recommendation was a two-year
9 contraceptive period, that was changed at the time of
10 the ethanol interaction being demonstrated to a two-
11 year contraceptive period, which is what is in place
12 in the European countries at this point in time.

13 Before the demonstration of the ethanol
14 interaction, there was no admonition about avoiding
15 alcohol because there was no awareness that that would
16 lead to a drug interaction.

17 MS. COHEN: But, you do have a consistent
18 program where the levels of what we used, and the
19 people who are being used? I mean, I'm feeling like
20 it's scattered all over the world, but I don't know
21 about the consistency in the follow through.

22 DOCTOR ARMSTRONG: Well, you should
23 appreciate that this drug has not been marketed in the
24 United States, so there is only clinical trial
25 experience in the United States with acitretin. There

1 is no other experience. So, we don't have that basis
2 for making that comparison.

3 CHAIRMAN McGUIRE: Doctor Kilpatrick.

4 DOCTOR KILPATRICK: Thank you, sir.

5 It's very rewarding for this committee
6 member to hear all of these questions being addressed
7 by other members of the committee. I may come back to
8 some of those to make the point, but since we have
9 that slide on the screen, Doctor Armstrong, do you
10 have the comparable slide with 95 percent confidence
11 limits on those levels and risks?

12 DOCTOR ARMSTRONG: We'll project it for you
13 in a moment.

14 DOCTOR KILPATRICK: Thank you.

15 That will illustrate why I was so violently
16 disagreeing with you when you were saying that the
17 five percent rate at the end was -- I heard that as a
18 deterministic statement, that was I was objecting to
19 it. These numbers, as you pointed out, are based on
20 very -- these figures are based on very low numbers,
21 with, as you can see, a very wide range of confidence.
22 So, I'm making the point again that I made earlier,
23 that we have very small numbers overall at individual
24 levels.

25 Going on from that, Doctor Lammer was

1 talking about, and you mentioned, sir, the relative
2 risk compared to what one would be expected by
3 coincidence. I used, as I suspect he used,
4 determining relative risks using a control group, and
5 I may come back to that in my final remarks.

6 By coincidence do you mean, as he said, the
7 historical -- what was in the literature, and why
8 didn't you not give relative risks as such? You
9 mentioned it but didn't give any figures.

10 DOCTOR ARMSTRONG: Okay, and let me answer
11 those progressively, because I did not mean to suggest
12 that because the incidence in this population was five
13 percent, that that was, therefore, a projectable or
14 conclusive for an entire population, but rather the
15 experience in this trial.

16 DOCTOR KILPATRICK: I understand.

17 DOCTOR ARMSTRONG: So, I'm glad we've been
18 able to clarify that.

19 DOCTOR KILPATRICK: Yes, except that I
20 would question your use of the word trial.

21 DOCTOR ARMSTRONG: Fair enough, in this
22 series of patients.

23 DOCTOR KILPATRICK: Yes.

24 DOCTOR ARMSTRONG: The second point that
25 you made was, what about relative risk, and what I'd

1 like to do is to go to the slide that shows the actual
2 malformations among the prospectively determined
3 studies.

4 When I mentioned relative risk, I did that
5 in the beginning when we were outlining ways in which
6 you might ascribe an association between the drug, or
7 a drug, or any risk situation, and a set of
8 malformations that did not exceed the background rate.

9 So, what we have done here is to say, if a
10 malformation that is described has any, any of the
11 features that are characteristic of the retinoid
12 syndrome, we have identified them with an asterisk.
13 And, therefore, we haven't tried to make a relative
14 risk argument on this.

15 DOCTOR KILPATRICK: I understand.

16 It was just a misunderstanding of
17 terminology then, okay.

18 Finally, and this point has been well made
19 by Doctor Cantilena, but I want to return to it again
20 on your slide ten, the excretion curve, if we can have
21 that, do you have that again with the ten individual
22 response slopes, curves given in that, or do you not
23 have that?

24 DOCTOR ARMSTRONG: I don't have a graph
25 that shows all ten individuals and what their levels

1 are.

2 DOCTOR KILPATRICK: Yes.

3 And, of course, the point here is that we
4 are, as you can hear, concerned, not what will happen
5 on average, but what some individuals who may be
6 untypical of this sample of ten, and is not
7 represented here, might experience, even if they are
8 compliant with the labeling directions.

9 Thank you, sir.

10 CHAIRMAN McGUIRE: Yes.

11 DOCTOR SMITH: Doctor Armstrong, I am
12 Doctor Deborah Smith from the Office of Women's Health
13 in the Commissioner's Office. I wanted to ask a
14 question about your 93 pregnancies terminated with no
15 information on the fetus.

16 DOCTOR ARMSTRONG: Right.

17 DOCTOR SMITH: Do you have information on
18 the -- any information on the time of exposures
19 associated with those pregnancies, notwithstanding the
20 lack of information about outcome and the distribution
21 of that timing of exposure?

22 DOCTOR ARMSTRONG: I'd like to ask Doctor
23 Maradit to answer that, please.

24 DOCTOR MARADIT: Yes, actually, we do have
25 some overheads. I cannot really give you exact

1 numbers from the top of my head, but we do have
2 distribution by pregnancy outcome.

3 DOCTOR SMITH: These are ones we have no
4 outcome. These are the cases where you've indicated
5 you don't have outcome, but it's -- these were the 93
6 pregnancies terminated with no information about the
7 status of the fetus or the fetal outcome, but I'm
8 asking, do you have any -- did you have any
9 information about the timing of exposure in those
10 pregnancies, and is there any information on the
11 distribution of that exposure?

12 DOCTOR MARADIT: Actually, there are some
13 tables in the package that you have, and in those
14 tables there are all the pregnancy outcomes and fetal
15 outcomes are distributed according to different time
16 intervals, including those cases, those pregnancy
17 terminations where no information was provided about
18 the fetus.

19 DOCTOR SMITH: Right, and I didn't go one
20 for one and count them up.

21 DOCTOR MARADIT: I can quickly --

22 DOCTOR SMITH: My quick look suggests that
23 they are -- there is some clustering, and I'm
24 concerned about how you -- what some of the plans may
25 be to fill in some of the blanks on the outcome data

1 in the future.

2 DOCTOR MARADIT: Our experience --

3 DOCTOR SMITH: And, I think some other
4 questions have also been asked or raised that,
5 perhaps, will come up later on, in terms of behaviors,
6 and information that might be ascertained as to the
7 circumstances under which people are making decisions,
8 even if you don't have actual pathology data at those
9 points in time.

10 DOCTOR MARADIT: I would like to actually
11 refer you to Doctor Lammer's comment about even in a
12 study -- setting up a study setting, even with active
13 effort, that it may not always be possible to actually
14 observe these fetuses from induced abortions or
15 spontaneous abortions, even with active effort to do
16 it.

17 And second is, one of our experiences was,
18 even in those prospective reports, there are some
19 birth defects that were detected from induced
20 abortion, so one of the functions that's usually
21 quoted is that if there would be an abnormal outcome,
22 but it would have been reported with the induced
23 abortions. This way one cannot generalize, but any
24 obvious malformations would have been reported to us
25 with pregnancy outcome as well.

1 DOCTOR SMITH: I'm accepting the
2 limitations on being able to actually have
3 characterization of anomalies under those
4 circumstances, but I guess what I'm asking about in
5 addition, as to whether or not there was any other
6 information ascertained about the characteristics of
7 those pregnancies, sans, the pathologic data, about
8 the individuals. It's a large number, a significant
9 number of the cases that were identified
10 prospectively, and is there any other information
11 about those cases that informs how one would like to
12 fill in some of the blanks in data, as well as informs
13 some elements in your educational approaches and
14 information to consumers and to prescribing
15 physicians.

16 DOCTOR MARADIT: Actually, the only data
17 that's blank with those cases is the fetal
18 information. Otherwise, in terms of why the pregnancy
19 has been terminated, or why the pregnancy, whether it
20 was a contraceptive failure, some age type of
21 demographic characteristics of these women, whether
22 they are patients following, they are routinely coming
23 there for their follow up, and the reason for the
24 pregnancy termination, all this information is
25 actually available.

1 DOCTOR SMITH: That's good, and, perhaps,
2 we would like to then have some considerations or have
3 a plan for some considerations about utilizing that
4 data in the planning for use of the drug.

5 DOCTOR O'CONNELL: If I could just make one
6 comment, Doctor Smith. If I understand correctly, you
7 would like to know for each of the time period cycles,
8 six-month time periods, in those time periods how many
9 was abortions?

10 DOCTOR SMITH: Well, that was -- I mean,
11 the original -- the original question just simply was
12 related to whether or not -- confirming that the
13 exposure time was identified and what the distribution
14 of those --

15 DOCTOR O'CONNELL: Right.

16 DOCTOR SMITH: -- 93 pregnancies was over
17 that exposure time, but notwithstanding that, and not
18 withstanding the issue of lack of pathologic data, I
19 think that having other kinds of information about
20 those 93 pregnancies, which do appear to be clustered
21 in the earlier stages after use of the drug, would be
22 very useful, would be helpful information to consider.
23 It's the pertinent positive, pertinent negative kind
24 of concept, still useful information in considering
25 information to consumers and information to

1 prescribing physicians.

2 DOCTOR O'CONNELL: Because I was just going
3 to point out under Tab 3 in the packet from the Agency
4 -- the first two pages there, you can sort of deduce.

5 DOCTOR SMITH: Right, and I did deduce.

6 DOCTOR O'CONNELL: Right, because almost
7 all of the no informations were --

8 DOCTOR SMITH: Right, no, I did deduce, but
9 thought that having deduced that, or anybody else
10 having deduced it, this was valuable information for
11 discussion and presentation, as I said, pertinent
12 positives and pertinent negatives are things to review
13 in planning.

14 And so, for example, data like
15 contraceptive -- use of contraception, but
16 contraception failure rates, is important, or is not
17 necessarily related to the determination and risks
18 related to teratogenicity, but it's certainly
19 important information with respect to coming up with
20 a plan for use of the drug.

21 CHAIRMAN McGUIRE: Doctor DiGiovanna.

22 DOCTOR DiGIOVANNA: I wanted to comment on
23 Doctor Mindel's suggestion of using plasma levels, or
24 repeated plasma levels, to get a sense as to a lower
25 body load of retinoid.

1 And, in one of the articles that we've had
2 in the package, actually looked at the ability to
3 predict plasma levels, to predict clearance, and it
4 turned out that plasma levels were a very poor
5 predictor of what you could measure if you measured it
6 directly in the fat.

7 So, I think that that, and in conjunction
8 with some of my experience in the distant past looking
9 at the elimination of etretinate after an individual
10 has taken it for many years, the pharmacokinetics are
11 very complicated. One of our experiences was that,
12 many years after stopping it, the same individual at
13 different times would display different half lives of
14 elimination.

15 What that was due to at the time wasn't
16 clear, we didn't collect information or expect to see
17 that. We would guess maybe it's due that at one point
18 they might have been losing weight, maybe some of this
19 was coming out of the fat.

20 So, if one was going to do that, I think
21 one would want to look at the real operative measure,
22 which is something like a needle biopsy of the fat or
23 something of that measure, I think would be fairer,
24 because I think you get a false sense of security by
25 saying a plasma level negative times two means you are

1 okay.

2 DOCTOR MINDEL: May I comment on that?

3 CHAIRMAN McGUIRE: Yes, go ahead.

4 DOCTOR MINDEL: I'm not saying that it's
5 safe if you have no level in your plasma. I'm saying,
6 as a minimal requirement, a minimal requirement that
7 you have no detectable at a 10^{-8} , 10^{-9} level, molar
8 level. Would you go along with that?

9 DOCTOR DiGIOVANNA: Oh, absolutely.

10 DOCTOR MINDEL: Okay.

11 DOCTOR DiGIOVANNA: I wasn't disagreeing.

12 CHAIRMAN McGUIRE: But, as John pointed
13 out, there is adequate -- there is abundant data that
14 speaks to this, in which there are negative plasma
15 levels, and there are stores in the fat. And so, the
16 other issue that we've not touched on is the threshold
17 level for embryopathy, and I don't know how close we
18 are going to be able to get to that.

19 We are running out of the morning, but,
20 Doctor Lammer.

21 DOCTOR LAMMER: Well, I just wanted to
22 follow up on those comments. I think the relevance of
23 the blood level is that that's what the fetus
24 experiences what the mother's blood level is. It
25 doesn't matter to the fetus how much is in the

1 mother's fat, unless pregnancy somehow brings more
2 etretinate out of the -- mobilizes it out of the
3 mother's fat, and I have no idea whether that's
4 possible or not, but that's the relevance of my
5 understanding of your comment, is there may be plenty
6 in the mother's fat, but what the fetus experiences is
7 only what's in the mother's blood.

8 DOCTOR DiGIOVANNA: Can I respond to that?
9 I think the concept is that what you are getting when
10 you look at the plasma is a window, a one-time event,
11 and that doesn't necessarily tell you what the
12 potential is for release of that compound.

13 And, I think with fat soluble compounds,
14 DDT had, I think, there is some experience in the past
15 with that, that levels could be leached out of body
16 stores if someone lost weight. So, I think it's not
17 a matter of it has to -- it probably has to go through
18 the plasma, but your measuring a negative level
19 doesn't mean that you are safe, it may be that those
20 levels may be high in the plasma under other
21 physiological circumstances.

22 CHAIRMAN McGUIRE: The simplest model would
23 be a three compartment system, the fat, the plasma and
24 the fetus, and the etretinate would like to be in the
25 fetus or in the fat. It really has no business being

1 in the plasma, that's just a transport.

2 And, as a transport, depending upon the
3 kinetics of that transport, that's either a trivial
4 observation or not, I don't know.

5 Let's see, Doctor Cantilena.

6 DOCTOR CANTILENA: Yes, just one small
7 comment in follow up, is just that, your statement
8 about, you know, what the fetus sees is really from
9 the bloodstream. It's probably more true for, you
10 know, low molecular weight, water soluble compounds.
11 In this case, and I was going to ask Doctor Bashaw if
12 he is aware of, you know, the amount of concentration,
13 for example, in the placenta or the trans-placenta,
14 you know, PK information for these drugs, because I
15 think it's actually significant.

16 And, really, I think the point that you
17 were making, John, is that you can have, in essence,
18 a redistribution with mobilization of fat stores or
19 increase, you know, metabolic rate, but then it's
20 extremely transient in terms of plasma concentrations.

21 But, the point that I would, you know, like
22 to hear about is, actually, what is the data for
23 accumulation in the placenta and then transfer across
24 the placenta for these, you know, class of compounds.

25 DOCTOR ARMSTRONG: We don't have the

1 information on that. However, one would expect, being
2 the placenta is very lipid-rich, that it's going to
3 function as a redistribution compartment, and that
4 it's going to, although maybe at low plasma levels, is
5 going to function as a storage site, and you would
6 expect very good or comparable levels to what you are
7 going to see out there in the fat, although there's
8 not been a concise study where we've gone and
9 collected placentas and looked at it. No one has done
10 that, to my knowledge.

11 But, just given the structure of it, and
12 the make-up of the tissue, one would expect that it
13 would function to draw out and become an additional
14 storage site, and you'd see, as you've mentioned,
15 mobilization, redistribution in tissues.

16 CHAIRMAN McGUIRE: Doctor McKinley-Grant,
17 this will be the last question of the morning, and we
18 will have an opportunity to discuss these issues this
19 afternoon.

20 DOCTOR MCKINLEY-GRANT: I actually won't be
21 here this afternoon, so I just want to make this
22 comment.

23 Doctor Mindel's comment, and Doctor
24 DiGiovanna, I see no problem, really, in getting the
25 two levels in a patient of the plasma and the fat, and

1 if -- I think what we've missed is, if the drug is
2 still present, that woman may choose not to get
3 pregnant. I mean, we know that we don't know that
4 much if it's not present, you know, and we don't know
5 the threshold, but I think it would be important to
6 include this in the criteria, along with the three
7 years, to have both levels. And, if there is
8 detectable drug, that the person would not get
9 pregnant until the levels were clear.

10 CHAIRMAN McGUIRE: Let's adjourn for lunch,
11 and try to be back as close to 1:00 as you can.

12 (Whereupon, the meeting was recessed at
13 12:15 p.m., to reconvene at 1:00 p.m., this same day.)

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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1 1:16 p.m.

2 CHAIRMAN McGUIRE: Let me introduce Doctor
3 Jonathon Wilkin. Jonathon, hi there. Doctor Wilkin
4 will discuss labeling decision analysis.

5 DOCTOR WILKIN: Is the machine on?

6 Okay. When one is about to make an
7 important decision, there are different processes that
8 one can adopt. I'm partial to the decision analysis
9 framework, and many of the aspects of this the
10 committee has already developed by asking questions of
11 the speakers this morning, establishing the context,
12 getting the facts down, what we know, what we don't
13 know, what we might know, and one of the pieces that
14 I will give is laying out some of the alternative
15 wording for the labeling, and then this will
16 eventually go the committee. The committee will make
17 a recommendation to us, by considering the
18 consequences of the different alternatives, valuing
19 what these outcomes might be, and then, of course,
20 recommending a choice.

21 Now, it is a decision, but it's a decision
22 on behalf of the public health, and whenever there is
23 a decision being made by representatives on behalf of
24 the public health or welfare, we must remember the two
25 fundamental postulates that exist.

1 It wouldn't be a difficult decision at all
2 if we didn't have trade offs to be made, and the
3 second part is that the well-being of society depends
4 on the welfare of its individual members.

5 So, in the committee's deliberation, as has
6 been the case with the sponsor and the FDA, we are
7 considering the women of child-bearing potential with
8 psoriasis who might benefit from this drug, the
9 children who might be born with drug-induced
10 teratogenicity, their families, communities, and also,
11 of course, the pharmaceutical industry.

12 Now, in considering this post-treatment
13 period of pregnancy avoidance, we would like to
14 achieve the right kind of balance. Of course, if we
15 are excessive, if we make it too many years, we'll end
16 up decreasing profit margin, and while we don't want
17 to just simply think in terms of dollars, there is a
18 very real issue here, and that is, industry is not
19 going to spend their resources to develop drugs if
20 there is excessively conservative labeling.

21 In some women, if we make this too
22 excessive, some women with psoriasis may unnecessarily
23 be deprived of Soriatane as their choice of treatment.
24 I think our colleagues from Roche and Ms. Rolstad,
25 from the National Psoriasis Foundation, were quite

1 eloquent on these points. Some unnecessary abortions,
2 abortions of normal fetuses might be performed if this
3 is excessive. Some women may experience adverse drug
4 reactions from unnecessary contraception. The rate of
5 adverse drug reactions from hormonal contraception is
6 very low, but it's not zero, and when adverse
7 reactions do occur sometimes they are very severe,
8 very serious.

9 And also, some women may unnecessarily
10 delay having children, that they would actually desire
11 having children, and they are approaching menopause,
12 and this is an additional cost that must be weighed.

13 Now, on the other side, if we have an
14 insufficient post-treatment period of pregnancy
15 avoidance, we will see babies born with an entire
16 spectrum of retinoid teratogenic injuries from
17 exposure to a known teratogen, and I would emphasize
18 the entire spectrum, it may not be just those babies
19 who represent the epicenter of the retinoid
20 embryopathy typology or syndrome, the babies that have
21 absolutely every kind of stigmata, and are easy to
22 make the diagnosis on, but there will also be babies
23 born that will have some of the less clear in the
24 isolated case representations that Doctor Lammer has
25 talked about.

1 And, some of the endpoints that Doctor
2 Lammer talked about would be very difficult to assess
3 actually at time of birth. They are things that one
4 would find out about later in life.

5 So, we want to achieve balance, and we want
6 to keep in mind what facts we know. We know that we
7 are talking about a drug that is in a pharmacologic
8 class that members of that class are teratogenic in
9 animals and man.

10 Soriatane is teratogenic in animals, it
11 leads to the classic retinoid stigmata. The lowest
12 teratogenic concentration in man is unknown, and it
13 actually may remain unknown. We might be faced with
14 that for many, many years, but there are other things
15 that we can learn that could still help.

16 Drug levels that are undetectable or
17 unmeasurable can still have biological effects. We
18 know this from other agents and other effects.

19 Etretinate is a pro-drug. It's converted
20 to the active metabolite acitretin, that may not be
21 100 percent of the message for etretinate, maybe there
22 are other metabolites that might be playing a role,
23 but, certainly, acitretin or cis-acitretin would be
24 the principal active, primary active metabolite.

25 Both etretinate and acitretin, there's

1 evidence that they are teratogenic in man. We know
2 that etretinate is more lipid soluble than acitretin,
3 and it is eliminated from the body more slowly.

4 And, we've also heard that acitretin can be
5 reesterified to etretinate in the presence of ethanol.
6 We don't know what other substrates other than ethanol
7 might contribute to this kind of reaction, if there
8 are other substrates that would donate two carbons,
9 or, perhaps, even different substrates that would form
10 different esters altogether that would still linger in
11 the adipose tissue. So, there's some areas that we
12 could learn more.

13 And then, Doctor Lammer has urged us to
14 look, not just at the extremely classic full
15 presentation of the retinoid syndrome, but also to
16 consider minor, and I use that in quotes, as being
17 less than the full expression, there still can be
18 extremely severe, very problematic kinds of findings
19 that in isolation, even though they are related to a
20 retinoid effect, they might be difficult to diagnose
21 as such in the individual case.

22 And so, when we are thinking about the
23 post-treatment period in which one would want to avoid
24 a pregnancy, we have to think of both the major and
25 the minor, and really, the models that we've been

1 thinking about have been based on the major, and that
2 may under-represent the time that would be required
3 for some of the more minor, more difficult to diagnose
4 presentations of retinoid growth injuries.

5 Now, the goal of labeling is to give
6 information. I mean, we want information in the
7 labeling that is important and relevant, and we also
8 want to give its level of certainty to the physician
9 and the patient, and let them decide.

10 Uncertainty is very difficult for our
11 species to work with. Jay Katz, and I think this is
12 actually an enjoyable read, I would encourage anyone
13 to pull this Hastings Centers report from February of
14 '84 and read Jay Katz's discussion of uncertainty in
15 medical settings, he talks about the denial of
16 uncertainty, the proclivity to substitute certainty
17 for uncertainty, as one of the most remarkable human
18 psychological traits.

19 And, if you think about this, just in daily
20 life, we make lots of assumptions. We don't have all
21 of the information, and we do pretty well with that.
22 It actually has great biological advantage for us to
23 make guesses. But, on some of the big ticket items,
24 it may not be in our best interest to fill in the gaps
25 prematurely.

1 The Lancet is unambiguous. They take the
2 view that the public should be told about uncertainty
3 when data with public health implications are
4 preliminary or inconclusive. And, it's the Agency's
5 view that the data that we have to date is helpful,
6 but it is preliminary, and it really is inconclusive.
7 Not that we are asking for perfect data, but there are
8 some things that can be presented that will help firm
9 up the model.

10 And, there are different discussions,
11 again, of uncertainly in clinical practice. This is
12 from an article by Logan and Scott in The Lancet.
13 Their emphasis is that doctors should recognize that
14 uncertainty is something they can share with their
15 patients, and that it's important for both to
16 recognize this.

17 Uncertainty is difficult in our present
18 medical system. Uncertainty means that the physician
19 is going to have to spend a longer period of time
20 discussing the pros and cons with the patient. The
21 patient will have to think about this longer, and many
22 questions will be asked, and it certainly would be a
23 quicker medical visit if we had some sort of two-line
24 statement in the labeling which was extremely
25 definitive, that would sort of answer everything.

1 The question is whether we actually have
2 that right now.

3 Now, there is a taxonomy of uncertainty,
4 and Renee Fox has described three categories. One is
5 incomplete or imperfect mastery of available
6 knowledge, and I don't think that's the case that we
7 have here. I think that our colleagues at Roche and
8 our FDA team can both pretty much agree on actually
9 what the data are.

10 There can be a difficulty in distinguishing
11 between that and limitations in current medical
12 knowledge, and we really think that limitations in
13 current medical knowledge is the type of uncertainty
14 that we are working with. There are some discreet
15 things that we could learn about pharmacokinetics,
16 about the esterification, about other substrates,
17 levels of detection, where it occurs in the body, what
18 happens, not just with a single dose, but with multiple
19 dose, with pharmacokinetics, we are not so much
20 interested in means, because means tell us how to
21 protect half of the population. I mean, we are really
22 interested, when we are thinking about teratogenicity
23 and carcinogenicity, of what the reasonable upper
24 limit might be.

25 And, again, the absence of evidence of

1 teratogenicity is not evidence of absence of
2 teratogenicity, and I would remind the committee that
3 it is really -- it's not the FDA, I heard mention of
4 the FDA doing studies, but it's incumbent upon
5 industry to provide this information to the Agency,
6 and then we review it, and our recommendation is based
7 on what has been provided to us by the sponsor. And,
8 if the sponsor chooses to provide additional
9 information to us, we certainly would formulate that
10 into a new model to generate labeling.

11 Okay. The labeling decision analysis. We
12 are talking about the period of time during which
13 pregnancy must be avoided after treatment is
14 concluded, and we have options that can be presented
15 as a decision tree. Remember that squares on a
16 decision tree are points, are notes of decision.

17 The first decision is, can we really say
18 anything at all, or should the label get the Tegison
19 label, the etretinate label, and just simply say it
20 hasn't been determined. And, our FDA team would hope
21 that that wouldn't be the committee's recommendation.
22 We believe that this is a safer medication than
23 etretinate. Our difficulty is knowing quantitatively
24 how much safer it is.

25 So, if we go down this pathway, where we

1 will actually say it is something, then we have two
2 choices. We can say a number of years, and that's
3 definitive, and Roche, of course, the sponsors, would
4 enjoy having something like this because they could
5 build their educational program on something extremely
6 specific. We share that belief also, that if they
7 have something specific, you can much more effectively
8 build an educational program.

9 The difficulty is, is that right now we
10 believe that that would be erecting an edifice on not
11 very firm a foundation, and our thought is that we
12 ought to say at least, and we would go for three
13 years, but that would be provisional. We could see
14 revisiting that as we learned more information, and we
15 could move this to the right level, whatever that is,
16 in the future.

17 Now, what does this "at least" mean to a
18 label? If we are saying avoid pregnancy after
19 discontinuing Soriatane for three years, that's really
20 clear cut. If this is the point in time when
21 Soriatane is discontinued, that means for three years
22 don't get pregnant at all, and after three years it is
23 okay. But, if we are saying at least three years,
24 what we are really saying, we know for the first three
25 years that that is not the best idea, and after that

1 we don't really know. It really is putting the
2 uncertainty into the label, but we can add to the
3 label as we learn more about patients that deliver,
4 and the outcomes of pregnancy, and as we learn more
5 about the enzymology and the pharmacokinetics, we can
6 craft that into the label to help this decision.

7 So, again, there is a corrigibility of the
8 labeling. The committee would not have to decide
9 today on once and for all labeling. It's quite
10 possible that we could have a decision process that
11 would take advantage of new information as it becomes
12 available and more definitively state in the future,
13 with greater certainty, what the risk is.

14 That will add more vegetation to the
15 decision tree, so that, if we get to, is at least
16 three years, and new information comes in, then we can
17 rethink, based on the data that come in, I mean, it
18 would be premature at this time to guess which pathway
19 we would go down, but the hope is that we would learn
20 enough information that we could go to a definitive
21 statement and that would help the sponsor build an
22 educational program.

23 Now, in Science there was a discussion
24 about breast cancer and about screening for breast
25 cancer, and a woman wrote in, in that particular

1 dialogue, she was not referring to this drug or
2 psoriasis, but I thought what she said was very
3 compelling and that is that, "Women are quite capable
4 of seeking out reasonable medical care, which will be
5 different for different women. We only need to hear
6 the evidence, the decision is our's." So, there are
7 many women who do want to know what we do know.

8 And, that's what the Lancet would describe
9 as the correct answer, "The public rightly wishes to
10 know about risks they take, and when don't know is the
11 correct answer, then that is what should be printed,
12 and anything else betrays the people's trust."

13 So, in conclusion, I will give you the
14 Division of Dermatologic and Dental Drug Products
15 recommendations for consideration by the committee.
16 The first is, is that we would like to encourage the
17 marketing of Soriatane. We believe it's a safer drug
18 than etretinate.

19 If we have not received from the sponsor
20 information that says that there is some special
21 advantage to keeping etretinate on the market, and so
22 in that circumstance, without having that information,
23 we would encourage the withdrawal of etretinate.

24 We would recommend providing Soriatane with
25 provisional, conservative labeling, until we have more

1 information about the variability and the
2 pharmacokinetics, more information on the enzymology,
3 the substrates, where it occurs in the body, and also
4 information on the patients who may deliver babies
5 over the next two, three or however many years we are
6 thinking about this. We would encourage the sponsor
7 to actively recruit women who are pregnant
8 prospectively, that is, before they deliver, so that
9 we can get the very best kind of information.

10 And then, we take this additional
11 information, and we can do this as soon as we receive
12 it, we can rethink the teratogenic risks and we can
13 also rethink the label, so that we can provide
14 Soriatane with more certain data-driven labeling
15 eventually.

16 CHAIRMAN MCGUIRE: Thank you, Doctor
17 Wilkin.

18 Are there questions? Doctor DiGiovanna.

19 DOCTOR DIGIOVANNA: I'm quite surprised to
20 see that the Agency is suggesting that, or
21 recommending, that Tegison be withdrawn, for a variety
22 of reasons, one of which is that it's a standard of
23 therapy for a large portion of the population. It
24 seems to have been used rather successfully.

25 There is some evidence, although it's

1 rather recent, and my own personal suspicion is that
2 each retinoid, while we think we know why it works, we
3 probably don't, it acts in a very heterogenous manner
4 for different diseases. For example, tretinoen, when
5 it first became available orally, was a welcomed
6 agent, and then when Isotretinoen became available
7 dermatologists said, well, this is a too toxic agent,
8 we've got another retinoid, we'll look for retinoid
9 responsive diseases and it was forgotten. It wasn't
10 until just a few years ago that it was identified to
11 be a very dramatic treatment for acute promyeolocytic
12 leukemia, where etretinate and Isotretinoen are
13 useless.

14 So, now that there's beginning to get some
15 dermatologic evidence that there are some diseases
16 which are thought to be responsive to etretinate, that
17 when they don't respond -- I'm sorry, failed to be
18 responsive to either drug, when they don't respond to
19 acitretin, do respond to etretinate, I would suggest
20 that rushing to remove what's a potentially useful
21 drug may not be the best road.

22 I was wondering if there was any specific
23 information as to why one would suggest that?

24 DOCTOR WILKIN: Well, what we would want to
25 hear from the sponsor, of course, is that information

1 that you've just described, and I think I mentioned
2 that, that if the case can be made that etretinate is
3 adding something in addition to what acitretin can
4 provide, then we would want to know what that is and
5 we would want to label it accordingly.

6 And, you know, while it says in there, it's
7 sort of -- if I just limited what I said to just the
8 words that are in the handout, it would have been a
9 four-minute discussion. I think I mentioned that in
10 the presentation, that if we can have that information
11 we'll certainly think about it.

12 DOCTOR DiGIOVANNA: But, in general, for
13 example, if a new non-steroidal anti-inflammatory drug
14 comes upon the market, do you suggest that other ones
15 be withdrawn, unless there's a particular reason for
16 them to be withdrawn?

17 DOCTOR WILKIN: Well, the particular reason
18 here, of course, is that etretinate is in the body
19 stores for a very long period of time, and let's just
20 suppose, it's not your belief, but if you'll assume
21 for the sake of discussion, that really, everything
22 that is good about etretinate is mediated through the
23 metabolite, acitretin or cis-acitretin, if you could
24 make that, you might make the decision to remove
25 etretinate because all it's really doing is sitting

1 around longer, and it possibly represents a greater
2 hazard if someone is having an untoward reaction to
3 the etretinate.

4 But, what we are really saying is, and I
5 wouldn't want this to become an etretinate meeting, we
6 want to focus on the Soriatane, is that if the
7 industry gives us information telling us how
8 etretinate can now be used with the approval of
9 Soriatane, we'd like to look that information over and
10 craft a different label.

11 DOCTOR DiGIOVANNA: I'm just surprised that
12 the assumption would be made that it is not useful.

13 DOCTOR WILKIN: Well, you know, I guess
14 that the FDA ought to be in Missouri, because we are
15 sort of "show me" type people. We would like to have
16 information one way or the other. It's not that we
17 are coming into this saying that it has no additional
18 value, we are asking for a demonstration of what
19 etretinate can accomplish beyond what acitretin can
20 accomplish.

21 CHAIRMAN McGUIRE: John, I liked your
22 comment that you didn't want to turn this into an
23 etretinate meeting. I think that's excellent, so
24 let's deal with the other issues.

25 Doctor Cantilena had a comment.

1 DOCTOR CANTILENA: Yes, actually, mine was
2 just in follow up to that, you know, just to say that,
3 I mean, and I guess I can see clearly why they would
4 suggest that, because from a standpoint, if, really,
5 you know, this is the active drug, and the other is a
6 pro-drug and has all the toxicity or, you know, the
7 down side, it makes absolutely perfect sense, and
8 actually there's another example that's just come up
9 with, you know, another drug class which is Seldane,
10 which is a pro-drug, and its active agent, you know,
11 is allegra, which is, you know, non-toxic. And, the
12 Agency, I think, is in the process of trying to get
13 the Seldane off the market.

14 I think there is a fairly clear parallel.
15 From a risk management standpoint, from the industry
16 side, why not go with, you know, a safer and effective
17 drug as opposed to exposure to the risk of having a
18 more toxic agent that sticks around for a long time.

19 CHAIRMAN McGUIRE: Doctor Lammer.

20 DOCTOR LAMMER: I guess I was born to try
21 and put genies back in the bottles too much, but we
22 are first being told that people really badly need
23 these drugs because they are so sick, and yet, we are
24 going to tell them to be off therapy for three years
25 and then another year to carry out a pregnancy. It

1 seems like contradictory logic.

2 Who is the target population to be treated
3 for this drug that they can be off their therapy for
4 four years to have a pregnancy? Is that realistic?
5 So, again, I'm trying to get the genie back in the
6 bottle. This seems unrealistic to me.

7 CHAIRMAN McGUIRE: We are not dealing with
8 the high school acne crowd, we are dealing with older
9 patients, and patients, many of whom are not in good
10 health.

11 DOCTOR LAMMER: Right, and wouldn't be able
12 to follow a recommendation probably even to avoid
13 conception for two -- or to be off the drug for even
14 two years and then carry out a pregnancy.

15 CHAIRMAN McGUIRE: Doctor Rarick, you had
16 your hand up.

17 DOCTOR RARICK: On a different note, I
18 don't if his was answered, I was wondering, Doctor
19 Wilkin, is the labeling proposed, I looked at it once
20 and I didn't see it, so maybe I missed it, do you also
21 propose that for patients with inadvertent exposures
22 during pregnancy, or who don't or aren't able to meet
23 this "at least three year" criteria, that there is
24 some information in there about level of risk, about
25 prenatal testing that can be done, about etretinate

1 levels that can be drawn, is there any kind of
2 counseling so that patients just don't see a big I
3 wasn't supposed to take this, I better terminate kind
4 of label.

5 DOCTOR WILKIN: Well, again, when one gives
6 recommendations, typically it is based on a database,
7 so that, you know, we know what outcomes can be
8 expected from different sets of, in this case, blood
9 levels or tissue levels.

10 We don't really have that kind of
11 information. I know earlier it's been requested that
12 we find out whether, you know, women still have the
13 drug on board. It's entirely possible that there's
14 drug on board at very low levels, and it really is not
15 a teratogenic risk. I mean, we cannot correlate any
16 levels with teratogenic risk.

17 CHAIRMAN McGUIRE: Doctor Buntin.

18 DOCTOR BUNTIN: I just wanted to comment on
19 Doctor Lammer's question. I would view Soriatane as
20 one of an armamentarium of agents we have to choose
21 from when treating patients with psoriasis, and often,
22 I'm a clinician, I see patients every day, you can
23 calm people down with one agent and control them with
24 something less toxic for their future.

25 So, it's not an absolute thing that you

1 have nothing else that you can ever use.

2 DOCTOR LAMMER: Well, I'm responding to the
3 -- and I know you don't want people talking about
4 etretinate, but when etretinate was approved I was
5 here for the hearing, and, basically, what was said
6 was that, women who have pustular psoriasis are so
7 sick off therapy, and that they don't have a relapse
8 when they go off etretinate, that they would be unable
9 to proceed for several years of waiting and still be
10 healthy enough to carry out a pregnancy.

11 So, it seems to me like we are -- it's kind
12 of playing a game, we are kind of saying, these are
13 really rules to live by for the people who prescribe
14 this drug for indications other than the approved
15 labeling condition, and that that's how they would be
16 recommended and managed. And, that makes me
17 depressed.

18 CHAIRMAN McGUIRE: Well, let me give you a
19 little therapy here. The rules were changed for 13
20 cis-retinoic acid. Initially, the rules were quite
21 stringent, and the patient had to fulfill several very
22 strict criteria.

23 Then, after several years, I can't remember
24 how many years, of experience, clinical experience
25 with 13 cis-retinoic acid, the rules were changed,

1 they were liberalized, and we moved into chronic
2 scarring acne instead of the initial definition of
3 chronic scarring and cystic acne. And, there were a
4 few other words that were changed.

5 I was not in on the original tretinate
6 deliberations, and I don't recall that language, I
7 can't speak to that.

8 Yes.

9 DOCTOR CANTILENA: Actually, just a
10 question for Doctor Wilkin. Do you have any, you
11 know, estimate for the off label use, in terms of all
12 of the retinoids, in terms of, you know, number of,
13 you know, prescriptions from like IMS versus, you
14 know, the incidence and, you know, number of patients
15 out there? Are there any surrogates that you could at
16 least, you know, try to take a guess at the degree of
17 off label use?

18 DOCTOR WILKIN: Yes. There's data that
19 would be available. I'll not hazard a guess, because
20 I'm not acquainted with those data.

21 CHAIRMAN MCGUIRE: Doctor Wilkin, I had a
22 question. Let's take a hypothetical. Let's say that
23 the Agency recommends that there be a three-year
24 moratorium on pregnancy, or a three year plus. Where
25 then is anyone going to get data on outcomes if this

1 population of women has no pregnancies? Are we going
2 to take pregnancies that occurred in advertently in
3 spite of pregnancy testing and education?

4 DOCTOR WILKIN: Well, sure, I think there
5 will be patients who will use the very best birth
6 control methods, and there will be failures, because
7 there are failure rates with the very best
8 methodologies.

9 And then, there will be women who will not
10 be completely compliant. They will not use the best
11 methods all the time, and so, pregnancies will likely
12 occur. I don't mean for this to sound like we are
13 going to wait for epidemiologic kind of data before we
14 would revisit the label. I think there are some
15 things that can be done with pharmacokinetics, and
16 learning more about this trans-esterification, so
17 there are really several areas where we could get more
18 information that would help the label.

19 CHAIRMAN McGUIRE: Yes, Doctor Orkin.

20 DOCTOR ORKIN: John, I don't know if it's
21 been quite addressed but, perhaps, somebody could
22 clarify. How long would one be on the Soriatane,
23 let's say, for women or anybody else, until the
24 condition is controlled well enough to consider
25 discontinuing and going to this three-year period? We

1 should have just a range or an idea.

2 DOCTOR WILKIN: Yes. I'm not sure we know
3 what dermatologists -- how they are using this in
4 Europe, that is, what length or period of time. Maybe
5 the sponsor has information on -- is this used for
6 like a year in a row, or two years in a row in some
7 patients?

8 DOCTOR ARMSTRONG: I don't think we have
9 information spontaneously reported to us that would
10 let us answer that question.

11 We do have some information from the
12 clinical trials done in the United States, where six-
13 month periods were provided, and then a drug holiday
14 was recommended or was part of the protocol, and then
15 people could take subsequent courses, depending on the
16 indication of reactivating of disease.

17 And, we had a number of patients in the
18 trials who went through multiple courses of treatment.
19 But, it's important to appreciate that the patients in
20 the clinical trials met very strict criteria for
21 eligibility, and the clinical trial design, of its
22 nature, imposed certain arbitrary options for the
23 patients.

24 So, we don't really think that we've got
25 experience from the clinical trials that would

1 necessarily translate to how it might be used for
2 particular patients in practice.

3 CHAIRMAN McGUIRE: Other questions for
4 Doctor Wilkin? Doctor Mindel.

5 DOCTOR MINDEL: Just to follow up what
6 Doctor Lammer said, I have a copy of the indications
7 of the labeling, and it does say that it's for only
8 severe, very severe, psoriasis. What is the labeling
9 for the new drug, Tegison, supposed to be? Is that
10 going to say only for very severe psoriasis?

11 DOCTOR WILKIN: It doesn't have the word
12 very. It says, severe psoriasis, and I believe the
13 words are, including erythrodermia and pustular
14 psoriasis.

15 DOCTOR MINDEL: Is it also going to say
16 that other therapies should have been tried before,
17 including et cetera, et cetera, the way this one does?
18 This one says it should only be used, you know, after
19 other therapies, other standard therapies, UVA Light
20 and so on.

21 DOCTOR WILKIN: Actually, do you want to,
22 Doctor O'Connell, let them know where it is in our
23 briefing package, and then you can read the data.

24 DOCTOR O'CONNELL: It's in your appendix,
25 under Tab 9, there's a copy of the label that has

1 everything that the sponsor and the Agency -- we've
2 settled everything except the issue we are discussing
3 today. And so, if you look on page one of the label,
4 it says, "Has severe psoriasis, and is unresponsive to
5 other therapies, or whose clinical condition
6 contraindicates the use of other treatments."

7 DOCTOR MINDEL: Does that mean that Doctor
8 Lammer's comment about it not being feasible to take
9 these patients, because it does sound to me slightly
10 different, but I'm not a dermatologist. Does that
11 mean that these are less severe cases, that these
12 could be people that would be off for several years,
13 and could be off the drug for several years and not
14 have to be forced to go back on the drug?

15 DOCTOR WILKIN: Well, you know, there are
16 dermatologists on the committee, and they can give
17 their opinion. It's been my experience that patients
18 who may have really severe psoriasis for several
19 years, that actually after that, whether it's a
20 regression towards the mean or exactly the natural
21 course of the disease or whatever, they seldom seem to
22 have extremely severe psoriasis for many, many years.

23 I suppose you could find one or two
24 patients that would fit into that category. That just
25 has not been my experience.

1 And then, Doctor Buntin made, I think, an
2 important statement, is that sometimes we'll use some
3 of the medications that normally we might keep on the
4 shelf, we'll use those to get patients under control,
5 and then we'll use some of the more common modalities
6 to maintain control.

7 CHAIRMAN McGUIRE: John.

8 DOCTOR DiGIOVANNA: Just another comment
9 with respect to that, is that very often
10 dermatologists that have a lot of experience in
11 treating severe psoriasis, because of the
12 tachyphylaxis that occurs with many treatments, and
13 because of the unique side effects of most of the
14 better treatments we have, tend to rotate treatment,
15 so it would not be unlikely for someone either to be
16 on Soriatane for a period of time, and then some other
17 drug, like light therapy for many years, or to be on
18 Soriatane plus light therapy for a period of time, and
19 then to be switched to some other therapy, in an
20 effort to sort of not overlap toxicities.

21 So, the situation you described would
22 frequently occur, where someone would be on it and
23 then be off of it for a few years.

24 CHAIRMAN McGUIRE: Doctor Armstrong.

25 DOCTOR ARMSTRONG: I'd like to add a couple

1 of points on that. First, there's a large amount of
2 clinical experience with Tegison that was not
3 available at the time the drug was originally
4 introduced, and we should take advantage of that
5 information in deciding how Soriatane might be used.

6 There's a converse to that, too, and that
7 is, some of the alternative forms of therapy are now
8 better understood than they were when etretinate was
9 being introduced. And, as an example of that, one of
10 the forms of therapy that Tegison says you should go
11 through before you consider prescribing it is PUVA.
12 We now have very recently published in the New England
13 Journal an indication that squamous cell carcinoma and
14 malignant melanoma are developing in patients who have
15 used those therapies.

16 We know already that patients who use
17 methotrexate long term may develop cirrhosis of the
18 liver, so the choice of any drug for a particular
19 patient is going to be influenced by their age. If
20 you have a 15-year period before melanoma or squamous
21 cell carcinoma is going to appear, that has a
22 different impact on a 20-year old patient than it does
23 on a 60-year old patient. So, you may end up with
24 differences there.

25 To Doctor Lammer's point, a patient who has

1 found other forms of therapy to be either less
2 effective or less readily tolerated than desired, and
3 finds that the retinoid is the preferred therapy, may
4 still wish to have a family and be prepared to take
5 sub-optimal control for a period of time in order to
6 have a child, and then make another decision about
7 what their therapy should be.

8 So, there are individualized grounds for
9 deciding who should get what therapy at what point,
10 and it's been our feeling that that kind of decision-
11 making should be done by the physician and the
12 patient, recognizing that half the population with
13 this disease is not at risk of teratogenic events, by
14 virtue of being males, and there are also a number of
15 women who are past child-bearing potential, post-
16 menopausal or whatever, or who are also not at risk
17 for having a teratogenic event.

18 So, trying to get the right balance among
19 those things is different for different patients.

20 DOCTOR ARMSTRONG: Can I also ask a
21 question of Doctor Wilkins?

22 DOCTOR WILKIN: Sure can.

23 DOCTOR ARMSTRONG: I particularly like the
24 approach that you take, and one of the things that I'm
25 concerned about is that we not be uncertain about some

1 things and not about others.

2 I don't know which slid of your's it is,
3 but there was a slide that showed a bar graph of three
4 years of contraception, and then what does after that
5 mean, could we go back to that slide for a moment?

6 DOCTOR WILKIN: Sure, could you -- could
7 someone move it all the way to the beginning, and then
8 I'll move it from the beginning.

9 DOCTOR ARMSTRONG: The concern that I have
10 is a very practical one, because we anticipate, based
11 on experience, be getting phone calls from people like
12 the practitioners on the committee, who use these
13 drugs to treat their patients, and we'll run into
14 through various scenarios patients who have, for
15 example, a contraceptive failure. And, I can readily
16 imagine an inquiry coming to my department saying, I
17 have a woman who has been taking Soriatane, understood
18 that there was an alcohol interaction and gave up
19 alcohol altogether, and tells me, assures me that she
20 has not taken any alcohol. She stopped the drug 30
21 months ago, and she now finds that she's pregnant.
22 What kind of advice would the current labeling
23 indicate should be given to that physician and to that
24 patient?

25 DOCTOR WILKIN: I don't think the labeling

1 is going to neatly summarize all of this in one pithy
2 aphorism that is going to work for everyone.

3 I think what we're trying to do with this
4 part of the label is inform women at the beginning
5 whether they intend -- they need to decide whether
6 they want to become pregnant, what is their risk for
7 becoming pregnant if they are going to really choose
8 effective birth control, and so, the first decision
9 node for women is, and for their physician, is should
10 they actually choose this particular treatment. And,
11 this is more to inform that particular decision node.

12 The information that should inform that
13 second decision node is really, right now it's a
14 pitifully small amount of information. A large part
15 of it is retrospective. I don't think there is a real
16 clear answer when a pregnancy what the actual risk of
17 teratogenicity is.

18 The risk of teratogenicity is what is going
19 to drive, ultimately, the woman's decision, because
20 women will not explicitly come up with an indifference
21 function, an indifference curve, where they are
22 saying, well, you know, for me the risk of having a
23 baby born with birth defects is 20 times worse than
24 aborting a normal fetus.

25 Now, they won't think through it that way,

1 but you can generate indifference curves that will
2 describe their behavior as if they did.

3 And, ultimately, the trade off between a
4 baby born with a birth defect and the abortion of a
5 normal fetus is a -- it's a direct trade off. If you
6 have a given rate of teratogenicity, which is
7 biologically defined, that's a variable that will not
8 be controlled by the sponsor or the Agency, that's
9 just part of the biology, if you have that, women
10 will, if they know what that rate is, then they can,
11 you know, make their decision based on that again, and
12 one can get a curve.

13 But, the trade offs will occur if any woman
14 becomes pregnant. I think the graph for the first few
15 years of this is probably to minimize the number of
16 women who are actually becoming pregnant by rigorously
17 working on the discussion of using birth control
18 methods, and many women will choose not to take the
19 drug simply because they don't want to embrace the
20 uncertainty.

21 And, I think that also is acceptable in the
22 beginning, while the sponsor continues to develop more
23 information about pharmacokinetics and the enzymology.

24 CHAIRMAN McGUIRE: Doctor Armstrong, did
25 you have another comment?

1 DOCTOR ARMSTRONG: Yes. I was just
2 concerned that where we do have information, we do
3 have 120 prospectively ascertained pregnancies, and I
4 recognize that we have a small number of those that
5 occurred more than two years after discontinuing
6 therapy, we have 11 of those cases, but we have no
7 birth defects among them.

8 And, if you look at the period within a
9 two-year period, the number of cases that we found was
10 actually five percent of the cases that were reported,
11 and I recognize that there is uncertainty in that
12 experience, but that also represents the entire
13 experience in two drugs that have been on the market
14 for a period of over 15 years between them, and how
15 quickly we are going to be able to provide additional
16 information from contraceptive failures or lapses in
17 contraceptive compliance in order to change the kinds
18 of experience, actual real-life experience, as opposed
19 to pharmacokinetics attempts to develop estimates.

20 DOCTOR WILKIN: Yes. Well again, maybe I
21 didn't make that sufficiently clear, that there are
22 three kinds of information, and I see the two pieces
23 that can be developed very early on would be the
24 pharmacokinetics, especially looking at the
25 variability, we are not so much interested in just

1 mean data, and the enzymology, understanding whether
2 different substrates could participate in this
3 esterification back to etretinate or an etretinate-
4 like drug, whether other metabolites of acitretin
5 other than the parent acitretin can do this, where in
6 the body the reaction could occur, considering the
7 limits of measuring these things in the assays, that
8 could be an improvement.

9 And so, we could have that even before we
10 get pregnancy outcome data. I don't think at any
11 point I said that this is all contingent upon
12 pregnancy outcome data. What I did say was that,
13 during this period of time, inadvertent pregnancies
14 would occur, and we could harvest that information and
15 craft it into the label as well.

16 CHAIRMAN McGUIRE: Doctor Orkin.

17 DOCTOR ORKIN: Just for completeness, we've
18 not mentioned what effect pregnancy itself would have
19 on psoriasis. I can see a scenario where a woman
20 becomes pregnant, gets severely worse during the
21 pregnancy, feels compelled to do something during the
22 pregnancy. It doesn't directly, but it's still
23 something I think we should address.

24 DOCTOR WILKIN: Well, for the committee, I
25 gather, or do you want an answer from the Agency? The

1 Agency is, we would like to develop a label which
2 would describe what we consider to be the best
3 rational use of a particular drug, based on the
4 information supplied to us by the sponsor.

5 Now, that's not to say that there might be
6 additional information that we haven't seen that would
7 support something different that's not reflected in
8 the label.

9 And, many times there are physicians who
10 will choose, and it's appropriate, because state laws
11 allow for this, they'll choose to use a medication off
12 label, it's really incorrect to say unapproved
13 because, again, most state medical boards provide for
14 the option of off label use.

15 And, what we're trying to describe is what
16 we think is the best use and convey that to inform the
17 patient and physician.

18 CHAIRMAN McGUIRE: Doctor Lammer.

19 DOCTOR LAMMER: So, if the Agency is
20 proposing a three-year waiting period for people
21 conceive, who is the Agency saying is responsible for
22 guiding that woman through that period of time, in
23 terms of providing her guidance about contraception?

24 DOCTOR WILKIN: Well, currently, the Agency
25 is silent on recommending someone other than the

1 practicing physician, the physician who prescribed the
2 medication originally. And, if the direction that you
3 are heading in is that that particular physician may
4 have a bias, is that your position?

5 DOCTOR LAMMER: No, I'm looking out for the
6 viewpoint of the woman, public health focuses on her,
7 who is responsible to her, is that the job of the --
8 is it not the job of the prescribing physician to
9 maintain follow up with her and take the primary
10 responsibility for keeping track of her contraceptive
11 practice and maintenance over that period of time?

12 DOCTOR WILKIN: No. Well, you know, one
13 could consider ethical imperatives and legal
14 imperatives. Legally, they are bound by what the
15 standard of practice is in their community.
16 Ethically, one could make a strong argument that they
17 should do just as you describe.

18 DOCTOR LAMMER: Well, I'm bringing it up
19 because it's been in medical journals, asking -- the
20 question has been asked in a number of letters to
21 editors, as to who is responsible, where does the
22 responsibility lie, and it strikes me that the Agency,
23 if they are going to make this recommendation, ought
24 to provide some guidance in that regard.

25 DOCTOR WILKIN: Well, you know, I think

1 this is something that the committee could also
2 consider and make a recommendation to us.

3 What our thoughts are in the short term,
4 which is three to five years, is that the sponsor
5 would actively enroll women who become pregnant and
6 prospectively found out, of course, ultimately, what
7 happens to their pregnancy.

8 CHAIRMAN McGUIRE: Ms. Cohen.

9 MS. COHEN: I was thinking when Tara
10 testified this morning of the great need for this
11 medication, not to belittle anyone who needs it, but
12 I personally feel so far I've heard a lot of things
13 about what has been done, but I don't really know with
14 whom they have done the testing. I don't know what
15 level of education, and with HMOs, and if they even
16 prescribe it, they are not going to spend time with
17 their patients.

18 You have doctors who are so busy, you can
19 wait in their office an hour or two, they need a lot
20 of counseling about this, and I think it's so serious
21 when you talk about birth defects. I was reading a
22 thing on the thalidomide, and that coming up again, I
23 think we are very cavalier, this is all about
24 patients. I heard Doctor Lammer finally talk about
25 patients, my husband is a scientist, I live with

1 science, but the end result is the patient and the
2 person who needs to be told what there is to do.

3 And, we all have different kinds of
4 behavior, and we have to, perhaps, do behavior
5 modification in order to do what's appropriate and to
6 wait two or three years.

7 I'm very concerned. I don't want to see
8 anymore birth defects of children in this country, and
9 this just might happen. And, I can -- I want to throw
10 in a plug too, because I think the food label has been
11 extremely effective, and I think among the things it
12 should be, it should be a drug label that's very clear
13 and very concise, and then further information along
14 the way, but we must have plain language, too.

15 CHAIRMAN McGUIRE: Yes.

16 DOCTOR CANTILENA: Actually, just a follow-
17 up question for Doctor Wilkin.

18 In the drug label, in the proposed label on
19 the drug interactions, are there further studies that
20 are planned? It talks about in that last paragraph
21 that there is an interaction between the progestin,
22 you know, -- preparation, that it interferes with the
23 contraceptive effect, are there other studies planned
24 to look at other kinds of contraceptive agents? And,
25 can you tell me what the mechanism is of that

1 drug/drug interaction?

2 DOCTOR WILKIN: Yes. In terms of, are
3 other studies planned, is the sponsor planning
4 specific studies in this area?

5 DOCTOR ARMSTRONG: Well, we believe that
6 there is a pharmacokinetics interaction, but in terms
7 of the pharmacodynamic endpoint, we don't see that the
8 pharmacodynamic endpoint was altered in the single
9 patient for which this has been described.

10 We have an extensive experience with
11 Isotretinoen and the use of oral contraceptives that
12 suggest that there is no interference, so, again, the
13 action item that we think is appropriate for this is
14 to say that there may be a difficulty with mini-dose
15 drugs, and that in selecting the effective form of
16 contraception that should be considered.

17 DOCTOR CANTILENA: So, you would recommend,
18 you know, the barrier method 100 percent? I mean, I
19 guess if -- I mean, I think as a prescriber it would
20 be very helpful for me to know that.

21 DOCTOR ARMSTRONG: Well, we recommend more
22 than one method. The intent is to use labeling that
23 is like the labeling used for Isotretinoen, and the
24 experience there is that using oral contraceptives you
25 get effective -- over whatever other technique is

1 used, you get an effective prevention of pregnancy,
2 because, as has been reported in the New England
3 Journal, the pregnancy experience with that program
4 has been better than the published series with other
5 techniques.

6 DOCTOR CANTILENA: Okay, so you are not
7 planning on doing any prospective like PK studies with
8 oral contraceptives?

9 DOCTOR ARMSTRONG: Correct.

10 CHAIRMAN McGUIRE: I think we are about
11 ready to go into this discussion. You had a comment,
12 go ahead.

13 DOCTOR SMITH: Well, I just wanted to be
14 clear that the response was relating to the use of
15 combined oral contraceptive pill as compared to the
16 issue raised about the use of a progestin only method,
17 and whether or not that response was speaking to other
18 progestin only methods, not just the -- or the
19 efficacy of other progestin only methods, not just the
20 so-called mini-pill or progestin only oral pill.

21 DOCTOR ARMSTRONG: The most extensive
22 experience that we have along these lines is from
23 Isotretinoin, and in that series most of the
24 individuals who selected alternative forms of therapy,
25 injectable or implantable, it represents a very small

1 proportion, so we really don't have as many. But,
2 within that, there is no indication that the failure
3 rate is higher with those implantable or injectable
4 contraceptives than with oral contraceptives.

5 CHAIRMAN McGUIRE: Doctor Armstrong, while
6 you are at the microphone, can you tell me the number
7 of pregnancies in the 13-cis retinoic acid program in
8 a given year, say '95 or '96?

9 DOCTOR ARMSTRONG: I can't give you the
10 number, I can give you the incidence rates, and I
11 can't give them to you precisely. What I can do is
12 give them to you in a relative sense.

13 In that survey, what has been clear is that
14 the educational message has been clearly received.
15 Ninety-nine percent of the patients recognize that
16 they should not take the drug when they are pregnant.
17 They need to avoid pregnancy and follow contraception
18 if they are taking the drug, and that the rates that
19 are seen compare quite favorably with reports of
20 contraceptive efficacy under ideal conditions.

21 So, the actual pregnancy rate is lower than
22 has been reported for general populations using oral
23 contraceptives, for example.

24 CHAIRMAN McGUIRE: And, roughly, how many
25 women are at risk?

1 DOCTOR ARMSTRONG: I think the --
2 epidemiology study is over 300,000 women enrolled at
3 this time, so there is a large number of women on whom
4 these data have been based.

5 CHAIRMAN McGUIRE: Doctor Lammer.

6 DOCTOR LAMMER: They enroll about 60
7 percent of women with new prescriptions per year, it's
8 on that order. It's not 100 percent of the women who
9 are prescribed the drug, but it's a sampling, I think
10 around 60 percent each year.

11 CHAIRMAN McGUIRE: Yes.

12 DOCTOR SMITH: I had one additional
13 question about the potential interest of the sponsor
14 related to contraceptive use and interactions, and
15 that has to do with any potential interest in
16 emergency contraception, in the use of oral
17 contraceptive pills for emergency contraception.

18 DOCTOR ARMSTRONG: I'm not sure what you
19 mean by, do we have any interest in that. We
20 recognize that that is a technique that is and has
21 been available to physicians. It's not something
22 that's part of our labeling, so we are not in a
23 position to be able to incorporate that in any of our
24 educational materials.

25 DOCTOR SMITH: Do you have a specific

1 reason for deciding against incorporating it into any
2 of your educational materials?

3 DOCTOR ARMSTRONG: We are not permitted to
4 do that, because it's not part of our labeling.

5 DOCTOR SMITH: You don't talk about other
6 contraceptive methods? You don't talk about needing
7 to use contraception?

8 DOCTOR ARMSTRONG: We talk about using two
9 effective forms of contraception.

10 DOCTOR SMITH: You don't describe them.

11 DOCTOR ARMSTRONG: Correct.

12 DOCTOR SMITH: I was asking about --

13 DOCTOR ARMSTRONG: I'm sorry, other than to
14 say that people who think that they had had
15 infertility need to use alternative methods, and that
16 tubal ligation may not be sufficient. So, people who
17 believe they are infertile, unless their basis for
18 that is that they've had a hysterectomy, need to
19 provide for contraceptive technique.

20 CHAIRMAN McGUIRE: Okay, thank you.

21 Well, we have some work to do, and I think
22 I'll open the meeting for discussion now.

23 Doctor Kilpatrick has cut his throat, I
24 don't know what that means.

25 DOCTOR KILPATRICK: 2:45 break, no, it's

1 2:15, sorry, sir.

2 CHAIRMAN McGUIRE: You cut your throat
3 prematurely.

4 Would you like to begin the discussion?

5 DOCTOR KILPATRICK: This is clearly a
6 lesson never to speak up, otherwise you are put on the
7 spot.

8 No, I wouldn't.

9 CHAIRMAN McGUIRE: Okay. Well, I can
10 always depend upon you to take a stand, and that's
11 good.

12 I think what we are dealing with is
13 precisely what Doctor Wilkin showed so clearly in his
14 slides. We have to decide what the risks are, based
15 on a very limited amount of data. We would like to
16 know what the embryopathy threshold is, and we don't
17 -- we really don't know that, and we're making some
18 major projections on the basis of 120 pregnancies that
19 have been followed and analyzed adequately.

20 I think that I could easily see us going
21 into a very conservative mode, or going into a very
22 liberal mode, and I think we need to wander around the
23 table and see what opinions we have.

24 We have a very limited amount of
25 pharmacokinetics. We have a limited amount of hard

1 data on the use of alcohol with this drug. We know a
2 lot about the chemistry and the partitioning of the
3 different forms, and so now I think we are ready to
4 discuss it.

5 Ms. Cohen.

6 MS. COHEN: I assume that everybody who has
7 a title of Doctor is going to be prescribing this, and
8 I think, can this be done by every doctor? You are a
9 doctor, too, of course you are.

10 CHAIRMAN McGUIRE: Jonathon, what is the
11 Agency's position on that?

12 DOCTOR WILKIN: If a physician is licensed
13 to practice medicine in any of the states or
14 territories of the United States, they will be able to
15 prescribe this medication.

16 CHAIRMAN McGUIRE: But, there have been
17 restricted drugs in the past, I think.

18 DOCTOR WILKIN: If you are talking about
19 limited distribution type drugs, Subpart H, I do not
20 know of any examples that exist today that are
21 currently available. I think the difficulty comes in
22 that even if that were something the Agency might be
23 interested in, it becomes an FTC type of issue.

24 CHAIRMAN McGUIRE: So, the answer to your
25 question is, once it's out there, it's out there?

1 DOCTOR RARICK: There can be voluntary
2 restrictions imposed by sponsors, much more simply
3 than a regulatory restriction.

4 CHAIRMAN McGUIRE: Okay, Doctor Orkin.

5 DOCTOR ORKIN: One of the implications of
6 Ms. Cohen's question has been addressed in the Sloan
7 information, in terms of in the Acutane, the division
8 of individuals who have the teratogenicity, those
9 prescribing were either dermatologists or primary
10 physicians.

11 Ed, you might have that information.

12 DOCTOR LAMMER: Ninety percent of the
13 prescribing physicians are dermatologists in their
14 study, in the patients we've followed who have gotten
15 pregnant on Acutane, 90 percent of the prescribers are
16 dermatologists, and I think that is reflective of
17 Acutane prescribing overall.

18 DOCTOR ARMSTRONG: I agree.

19 DOCTOR BUNTIN: But, don't you think that
20 just reflects the utilization of the drug? I mean, if
21 dermatologists are going to prescribe it more, we are
22 going to have more incidences of foul ups. And, I
23 know no dermatologist would intentionally enroll
24 somebody they thought was going to get pregnant.

25 And, I've a heavy Acutane user, I'm not

1 saying that to get me comments or credits, but you try
2 to establish a relationship where you decide that you
3 feel you can trust this person to follow instructions,
4 and most dermatologists I know will have more than one
5 visit to make that decision, for at least Acutane,
6 Tegison or whatever you have. You don't immediately
7 prescribe it until you get a feeling for the patient,
8 and there are some nice informational pamphlets. We
9 have consent forms that we can use, too.

10 So, I put this on the scale with any drug
11 that has risk and benefits, and you make that decision
12 one on one with that individual patient.

13 And, for Ms. Cohen, I mean, part of being
14 a physician is that you get to prescribe drugs which
15 have severe side effects, and you just hope you choose
16 patients and doctors wisely.

17 MS. COHEN: Okay.

18 And, you also hope the physician gets their
19 information somewhere besides the detail man who comes
20 to sell it.

21 DOCTOR BUNTIN: That's true, and one more
22 comment about practicing today, you often have the HMO
23 deciding whether or not a drug can be written,
24 because, for example, with Sporanox, primary care
25 doctors will refer to me, they'll send people to me to

1 make the decision can they get Sporanox, which is an
2 anti-fungal, because they can't prescribe it. They
3 won't fill it if it's written by a non-dermatologist
4 now. So, we have that little element of medical
5 practice to deal with, too.

6 CHAIRMAN McGUIRE: John.

7 DOCTOR DiGIOVANNA: This has been a very
8 interesting set of literature, and it's been a very
9 interesting discussion. And, the way that I come down
10 on it is, the question we've been asked is, how long
11 after stopping Soriatane treatment should a woman
12 avoid becoming pregnant. And, quite clearly, we have
13 some information, but in my view we don't have enough
14 information to pinpoint a specific date, and I think
15 that date is going to be different depending upon the
16 woman, how much of the drug, and how she's taking the
17 drug, and how much alcohol, and certainly the
18 intrinsic variation we see in metabolism.

19 And, clearly, all of those issues are not
20 dealt with. I'm reassured to some extent that from
21 the pregnancy data that it looks like there is not a
22 lot of teratogenic outcome in the 24 months experience
23 post etretinate and post acitretin.

24 However, I'm impressed by the results of
25 one study that showed that etretinate was detected in

1 the plasma, in fact, 52 months, in plasma. And, given
2 the poor understanding of the pharmacokinetics curves
3 and how they vary between individuals, I think that
4 the recommendation of the Agency, that at least three
5 years is a very reasonable and prudent one, and I
6 think it's a real middle-of-the-line thoughtful
7 consideration. I think that knowing that a very
8 reasonable amount of pharmacokinetics data could show
9 that the range of responses that people have for
10 holding on to etretinate is either going to be very
11 wide and of more concern or very narrow and little
12 concern could lead to a downward adjustment of that.
13 I think that that's reasonable.

14 The only addition I could have, and I don't
15 have a good wording for it, is whether or not the
16 wording could be slightly more -- could convey
17 slightly more information, possibly to suggest or to
18 add the information on the pregnancy outcomes, in that
19 while we would recommend at least three years, that
20 the period of information over 24 months there have in
21 women -- so many women who have been exposed, there
22 have not been known teratogenic outcomes, to convey
23 the information that while it's wise to not do this,
24 that the risk that's involved is a diminishing risk,
25 and that the risk while you are taking the drug is

1 large, that, yes, I'd like to know definitely two
2 years or three years I'll be clear after that, I won't
3 know that, at least I'll know if the magnitude of the
4 risk is a continually diminishing one.

5 CHAIRMAN McGUIRE: Okay.

6 I like your argument, and I like your
7 thought, and how did that argument and logic take you
8 to three years, instead of two years?

9 DOCTOR DiGIOVANNA: I think 52 months
10 observation is longer than three years, and if we have
11 an observation of 52 months, both in the plasma and in
12 the fat on a few individuals, I think that knowing
13 that we do not know the spectrum of looking across
14 ethnic populations and looking across enzyme
15 variations, I think that that's a sense that at least
16 a portion of the population is going to hold onto this
17 drug for more than three years.

18 And, I don't know if that's going to be a
19 common event or a rare event, and I think it raises a
20 flag to me that I think two years, there are clearly
21 larger levels, and while we don't know what the
22 teratogenic threshold is, we know it's a teratogen.

23 In the initial stages, I would agree with
24 Doctor Lammer, that a teratogenic outcome is something
25 significant to be avoided at all costs, and to err on

1 the side of time until an additional piece of data --
2 again, one of the difficulties here that the Agency
3 has raised, and that I'm concerned about, is that I
4 don't know the spectrum across the population as to
5 whether that 52 months is a common event, or whether
6 it's a rare event, or whether we may find that ten
7 percent of the population hangs onto it for more than
8 that.

9 I think that's easy information to obtain,
10 but I think it leaves me with a sense of uncertainty.

11 CHAIRMAN McGUIRE: Thank you.

12 Other comments? Yes, Doctor Orkin.

13 DOCTOR ORKIN: Although I understand the
14 reasoning, John, I'm uncomfortable with that. I think
15 it adds confusion to the individual involved. It kind
16 of clouds up the issue.

17 DOCTOR DiGIOVANNA: How would you uncloud
18 it?

19 DOCTOR ORKIN: By leaving the sentence out.

20 DOCTOR DiGIOVANNA: Oh, the additional
21 information.

22 DOCTOR ORKIN: Yes.

23 CHAIRMAN McGUIRE: Yes, Doctor Mindel.

24 DOCTOR MINDEL: The only recommendation
25 that I feel comfortable with is the one currently that

1 is with Tegison. It says, "The period of time during
2 which pregnancy must be avoided after treated is
3 concluded has not been determined."

4 This new drug is really a low dose of
5 Tegison, that's what you are giving, baby aspirin,
6 adult aspirin, you are giving a low dose of the same
7 drug.

8 And, it hasn't been determined -- if the
9 FDA had proposed four years instead of two, I think
10 you would have, for the same reasons, said, well,
11 that's eminently reasonable. But, why four, why
12 three, we don't have the information. And, I think we
13 are doing a disservice if we do.

14 If we are going to make any recommendation,
15 I feel more comfortable about a blood level that's
16 measurable, and saying at least when it's not
17 detectable by an assay that can measure 0.1 nanograms
18 per ml. And, I would like that incorporated into a
19 recommendation.

20 CHAIRMAN McGUIRE: Let me question one
21 remark you made, which is that, giving acitretin is
22 like giving a small dose of etretinate. I'm not sure
23 we know that. We have demonstrated, or etretinate has
24 been demonstrated in subcutaneous fat and in the serum
25 of individuals who had received acitretin, but it's my

1 understanding that that, so far, has been associated
2 only with ethanol intake.

3 Is that correct?

4 DOCTOR WILKIN: Well, that doesn't mean
5 that ethanol is the only thing that can do it, it's
6 just that's the information that we have at present.

7 CHAIRMAN McGUIRE: Yes, okay.

8 DOCTOR WILKIN: Well, I think the reason
9 that committees are formed is to make decisions on
10 incomplete information.

11 CHAIRMAN McGUIRE: Yes, Doctor Kilpatrick.

12 DOCTOR KILPATRICK: When you have complete
13 information you ask a statistician.

14 MR. BASHAW: That's the last resort.

15 DOCTOR KILPATRICK: I'd like to ask, Mr.
16 Chairman, whether we can discuss the other aspect of
17 Doctor Wilkin's proposal. He said clearly that any
18 recommendation that we made might lead to a
19 provisional label, and that, hopefully, the sponsor
20 would engage in ongoing research after the drug was
21 made available in the United States.

22 I've been thinking about such a study, and
23 I cannot honestly see how such a study, even a well-
24 conducted study, and I can have more to say about
25 that, could be conducted in a short time.

1 So, I think that the provisional
2 recommendation that we make, if adopted by the FDA,
3 will be, in fact, in operation for quite some time,
4 and I just wanted to bring that element up while we
5 consider what the label should be.

6 CHAIRMAN McGUIRE: I agree with you, and
7 that was the reason for one of my earlier questions,
8 which is, I think we will depend upon the perspective
9 ascertainment, but a sponsor of a pregnancy that
10 occurred while individuals are either taking the drug
11 or have many months away from the drug.

12 CHAIRMAN McGUIRE: John.

13 DOCTOR DiGIOVANNA: Just for the sake of
14 the whole Advisory Group's understanding, and to
15 clarify for myself, I wonder if someone from Roche
16 might be able to tell us, and I don't know if you have
17 all this information, but it might be easier than I
18 think it is, a sense as to, roughly, how many
19 countries etretinate is available, and what the
20 contraceptive limit is, and how the regulations for
21 etretinate, the package insert for etretinate in the
22 U.S., compares to that.

23 I believe the U.S. period, the indefinite
24 one, that this may be the only country that has that,
25 and that in most countries it is two years.

1 DOCTOR ARMSTRONG: Canada, actually, has
2 labeling very similar to the United States. The rest
3 of the world has two years as the recommendation for
4 Tegison, and the experience that we presented with the
5 prospectively ascertained pregnancies represents the
6 entire combined world experience with both drugs.
7 And, that's over 20 years of marketing of the two
8 drugs.

9 So, I think your point is well taken, that
10 there isn't going to be any dramatic increase in the
11 number of patients for some time.

12 DOCTOR DiGIOVANNA: So, the labeling that
13 -- the stringent labeling, conservative labeling we
14 are suggesting here, of at least three years, is for
15 acitretin, is more conservative than most of the rest
16 of the world has for Tegison.

17 DOCTOR ARMSTRONG: Correct.

18 CHAIRMAN McGUIRE: Doctor Smith, did you
19 have a question?

20 DOCTOR SMITH: I was just confused for a
21 moment, and to be sure I understood, because your
22 worldwide experience -- excuse me, I put a mint in my
23 mouth --

24 CHAIRMAN McGUIRE: That's why I called on
25 you.

1 DOCTOR SMITH: -- the worldwide experience
2 reflected -- this is the spontaneous reports, and I
3 would -- I'm sitting here, I want to be sure I'm not
4 interpreting or misinterpreting that there might not
5 be other options for being able to gather pregnancy
6 related data, other than relying solely on spontaneous
7 reports, as in speaking to one of Doctor Wilkin's
8 comments before about attempting to be more assertive
9 about developing a registry and having the outreach to
10 both users and physicians to increase the reporting of
11 pregnancies and the prospective evaluation.

12 DOCTOR ARMSTRONG: The information that we
13 have is what has been reported to us. I'm not aware
14 of any other mechanism that's in place around the
15 world.

16 DOCTOR SMITH: Well, I think the question
17 is not what is in place, perhaps, now, but also what
18 could be in place in trying to address this issue of
19 what would happen in terms of obtaining more
20 information under the flag of a provisional labeling
21 for some time to come.

22 DOCTOR ARMSTRONG: Well, we could discuss
23 what that might look like and how that might be used.

24 DOCTOR KILPATRICK: I have some comments.
25 I will have some comments when we get to that point,

1 but with your direction, Mr. Chairman.

2 CHAIRMAN McGUIRE: Go right ahead.

3 DOCTOR KILPATRICK: I thought -- do you
4 think it's appropriate to talk about further studies
5 before we --

6 CHAIRMAN McGUIRE: I think the better our
7 understanding of future studies and surveillance, the
8 more comfortable we are going to be making whatever
9 decision we wind up making.

10 DOCTOR KILPATRICK: Actually, the sponsor
11 and members of the committee should realize that I
12 come from a tradition in which design of experiment is
13 much taught. Sir Austin Bradford Hill, many, many
14 years ago, brought in the gold standard of the
15 randomized clinical trial.

16 It's not possible, given that this drug has
17 been approved by the FDA, to have a randomized
18 clinical trial, and so what I'm going to suggest is
19 the next best thing, whether or not it is feasible is
20 to be decided by the sponsor and the Agency.

21 I want to talk about a hybrid study, that
22 is, a cast control study and a cohort study. And,
23 what I'm suggesting is that the sponsor consider
24 starting an international study, and it has to be
25 international because of sample size considerations,

1 following patients, that is, women with psoriasis, who
2 elect to be treated with this drug or elect not to be
3 treated with this drug, that is where the
4 randomization is, obviously, not coming into action,
5 and then followed over many years, and pregnancies
6 documented, and then out of those pregnancies some
7 congenital malformations will arise, both in the
8 treated and untreated women.

9 And then, the hybrid nature of this study
10 is that, since these are rare, it might be good to do
11 a case control study of the individuals who have
12 delivered a congenital malformed baby, the whole
13 question of spontaneous abortions or terminations of
14 pregnancy is something I haven't considered, and that
15 case control study is an effective way of looking at
16 the data assuming that you have many of one type and
17 few of another. I don't really know which of one type
18 you'll have, whether you'll have more malformations in
19 the untreated versus the treated women, the women
20 treated with Soriatane.

21 However, as relevant to my earlier remarks,
22 this is going to be expensive, and it will take some
23 time, and there are many aspects of this, but I just
24 wanted to put in my -- worth at this time, because I
25 think that it will take some time before such a study

1 or some equivalent of that can actually get estimates
2 with appropriate confidence limits on the actual risk
3 of a woman who becomes pregnant after the taking of
4 Soriatane to deliver a malformed baby.

5 CHAIRMAN McGUIRE: Yes.

6 DOCTOR GUINEE: I'd like to ask Doctor
7 Lammer his feeling about this situation, in terms of,
8 does this look like we have more defects than you'd
9 expect in a population in general? How do you
10 interpret the data, since most of the defects are not
11 characteristic of drugs in this class? Are we making
12 a decision on the basis of lack of data, or using the
13 data?

14 DOCTOR LAMMER: I'll try to address two
15 different points, first Doctor Kilpatrick's suggestion
16 about a case control study to look at this problem.

17 We went down that road a while ago, and
18 we've even published a paper talking about the pros
19 and cons of different research strategies to address
20 how significant from a public health viewpoint this
21 problem might be, particularly, really with a focus on
22 retinoic acid embryopathy, and I'd be happy to send
23 you that paper later. But, it's a resounding,
24 unenthusiastic response. I don't think a case control
25 study is the route to go.

1 I think the --

2 DOCTOR KILPATRICK: Is that because it
3 lacks par, was the sample size big enough?

4 DOCTOR LAMMER: It's because it's an
5 extremely rare exposure, and because none of the
6 individual malformations that you could ascertain on
7 is characteristic enough of the syndrome to really do
8 the job.

9 But, we've gone through a whole analysis of
10 the pros and cons of that approach with retinoic acid
11 embryopathy, and, I mean, the attack rate is high
12 enough that it's feasible to approach this from a
13 cohort study viewpoint. I think it just -- the
14 success of that depends on the rigor with which you
15 conduct that study and the depth with which you look
16 for the adverse outcomes of the pregnancy.

17 DOCTOR KILPATRICK: I don't want this to
18 become a discussion between two members of the
19 committee, but I did suggest a cohort approach, and
20 tried to explain the case control aspect in a cohort
21 situation. I called it a hybrid study.

22 DOCTOR LAMMER: I see, okay.

23 DOCTOR KILPATRICK: Right.

24 DOCTOR LAMMER: Okay.

25 With regard to interpreting the data that

1 Doctor Armstrong presented, I think it's just -- I
2 think it's unequivocal, or I think it's equivocal. I
3 don't think you can really interpret it very strongly
4 one way or the other.

5 The five percent malformation rate among
6 the kids exposed whose mothers got pregnant in the two
7 years following their stopping the drug is clearly on
8 a point estimate basis a little higher than the
9 background risk I would expect of two to three
10 percent, but is it truly different based on the number
11 -- the size of their study? I suspect not. So that,
12 I think that we are left with uncertainty as to
13 whether that's really an increase or not. It's
14 certainly not a decrease, it's either within the
15 expected number or else it is a small increase, but
16 the numbers just aren't there to really draw a firm
17 conclusion.

18 I don't think I can say anything more about
19 it than that. I think it's inconclusive, based on
20 small numbers.

21 Also, a few other things?

22 CHAIRMAN McGUIRE: Please.

23 DOCTOR LAMMER: It's difficult -- well, as
24 I said before, I think the genie is out of the bottle,
25 etretinate is out there, and I don't see strong

1 reasons why -- this drug clearly seems superior to me,
2 I mean, as Doctor Bashaw pointed out this morning,
3 etretinate has bazaar pharmacokinetics properties.
4 There just aren't very many medications like it out
5 there, and it probably should have never been approved
6 because of its strange properties in the first place,
7 and this drug seems better to me. It's hard to make
8 a case that it's worse. It can only be better than
9 having etretinate available.

10 I personally have always advocated for this
11 whole class of drugs that they be significantly
12 restricted in their distribution, but that's not a
13 position that's been embraced even remotely by the
14 manufacturer, and I don't see it happening again.

15 But, it's hard to believe that this drug is
16 going to be a bigger problem than etretinate is. It
17 looks like it is better.

18 CHAIRMAN McGUIRE: Other comments?

19 DOCTOR LAMMER: I also, as I said this
20 morning, two other things, I feel the Agency and this
21 committee ought to make a statement about who is
22 responsible to these women, and I think it's the
23 prescribing dermatologist needs to be legally and
24 morally responsible for keeping track of these women
25 after they are off therapy for that period of time.

1 They can't just be left loose and unmonitored.

2 And secondly, I think the handful of women
3 who have consulted me about pregnancy in this
4 situation all want blood levels done, and somebody has
5 got to be responsible for providing that. And, so far
6 the women I've talked to have been refused by
7 Hoffmann-La Roche to be provided that service, and I
8 think they deserve it.

9 CHAIRMAN McGUIRE: Okay.

10 Let me respond to two things. I think the
11 dermatologists and Roche have done a pretty good job
12 of educating each other in the use of Acutane, but,
13 remember, that's a five-month deal, and we're talking
14 about a two to three-year period here. That's going
15 to be much more difficult, much more difficult.

16 You've seen the documents that the patients
17 read, and sign, and take home, and come back and
18 discuss with the dermatologists, that takes -- that
19 times time, and I think most dermatologists take that
20 time because we feel at risk, we are providing a
21 service and we feel at risk.

22 Something else more complex is going to
23 have to be put in place, and I don't know, Doctor
24 Armstrong, if there is a registry for acitretin in any
25 country if anyone is tracking these patients.

1 DOCTOR MARADIT: There have been several
2 efforts, actually, especially in France and in the
3 U.K., both by Roche and by the regulatory authorities
4 in specific countries as well, to really achieve --
5 get cohorts of patients, users and looking at
6 outcomes.

7 But, all of these efforts failed, because
8 what happens is that, because of the risk of
9 teratogenicity it's estimated that about 13 percent of
10 the users end up being women of child-bearing age, and
11 of these women, which is, you know, nine of the same
12 age range, constitute about 40 percent of the male
13 users, whereas, women of the ages 15 to 45 constitute
14 only 13 percent of the total users, or approximately
15 25 percent of all female users. So, there is an
16 intentional, or I shouldn't say intentional, but there
17 is a cautious attitude by the prescribers not to
18 prescribe less or to prescribe the drug to women of
19 these ages. So, this is the population that we are
20 looking at.

21 Then, there is the birth rates in
22 individual countries, which is about, you know, in
23 western Europe it's about 1.5 percent of the yearly
24 birth rate in a cohort, so this means these women are
25 plus using oral contraceptives, so there is the

1 conscious efficacy coming into the place, so what
2 happens is that, even though there would be a cohort
3 of users, in the end the number of women who come to
4 the point of getting pregnant turns out to be
5 extremely low. So, that's why all of our efforts, and
6 even of the regulatory authorities in individual
7 countries, their efforts failed because of limitations
8 of achieving the required sample size.

9 CHAIRMAN McGUIRE: Okay, thanks very much,
10 that's also encouraging.

11 I really don't know what to do with this
12 blood level thing, which represents largely, I guess,
13 the fact that I don't -- I can't imagine that it's
14 good to have a high plasma level, but I don't know
15 what having a low plasma level means, since the
16 lifetime of the material in the plasma I think is very
17 short and it's on its way somewhere to somewhere else,
18 and it just happens to get caught in the middle.

19 I think, yes, that's what I'm going to do,
20 we are going to take a 15-minute break, and we're
21 going to talk about that when we come back. Fifteen
22 minutes.

23 (Whereupon, at 2:52 p.m., a recess until
24 3:20 p.m.)

25 CHAIRMAN McGUIRE: Let's be seated.

1 We have a single question to address, and
2 the question is, how long after stopping Soriatane
3 treatment should a woman avoid becoming pregnant?

4 Now, there will be a certain number of
5 footnotes and appendages that will go along -- or
6 appendices that will go along with this, and we can
7 take them as they come. I can do something daring and
8 tell you how I feel, and I realize that can turn a
9 committee around the other way and, perhaps, it will,
10 but if it does that's okay.

11 I don't much like the wording one year, two
12 years and whatever, I think we should attempt to
13 provide a cut off, and at the same time indicate to
14 the prescribing physician and to the patient that
15 we're basing our decision on limited information.
16 And, there should be some sort of agreement between
17 the sponsor and the Agency that the ascertainment
18 process will proceed, and that we will have an
19 opportunity to see what data they collect on plasma
20 levels after the drug is discontinued over the ensuing
21 years.

22 So, my concern is that we have a drug out
23 there, etretinate, that I would, as a practitioner and
24 as a member of this committee, I would really like to
25 see replaced with acitretin, and so I don't want to

1 make the rules for acitretin so stringent that we
2 continue with etretinate as a major drug.

3 Having said that, I think I would tell you
4 my position in terms of numbers, and, that is, I would
5 recommend that there be a three-year moratorium on
6 pregnancy, and then after the three-year moratorium
7 indicate that we've made that decision based on
8 limited data on the 120 pregnancies that were
9 prospectively analyzed.

10 That's the most I've said today. Let's go
11 around the room. Where can I start? John.

12 DOCTOR DiGIOVANNA: Again? I'm not sure
13 about the semantics, and I'm not sure what semantics
14 would best serve the public, the Agency and Roche.
15 I'm a little concerned about coming down, as you
16 suggest -- about explaining, as you suggest, or
17 stating that a three-year period of time was
18 determined on the basis of limited information of 120
19 prospective pregnancies, because I think that as
20 Doctor Wilkin suggested, the absence of evidence of
21 teratogenicity is different than the evidence of
22 absence of teratogenicity. I may have that backwards,
23 but, at any rate, I think that gives me a sense of
24 comfort. It doesn't give me a sense of out of 20,000
25 pregnancies we would not see an elevation above the

1 baseline.

2 I think that this information is also
3 based, not only that, or the three-year period would
4 be based not only on that, but also on what we know
5 about the pharmacokinetics. In fact, I think the
6 pharmacokinetics makes a stronger case for picking a
7 time period, a two-year or a three-year time period.

8 What we don't have is a full understanding
9 as to the parameters of the conversion of acitretin to
10 etretinate, and I think that's where the difficulty
11 with picking a date lies, and with picking a way of
12 conveying the risk.

13 My main concern is that I would rather err
14 on the side of omission than commission, and I would
15 rather say that we have - the evidence that we have
16 suggests that pregnancy should not take place for at
17 least three years, rather than to not give adequate
18 information. I would think that giving someone the
19 impression that the three-year period is a safe period
20 allows for the post-three-year period to be fraught
21 with someone feeling, I'm safe, and I'm not going to
22 run into trouble with this, and then when they do I
23 would take a sense they have been misled where the
24 information was available, and I would find that more
25 offensive than the degree of uncertainty.

1 I think the uncertainty is something that
2 we have every day with many diseases, and we're
3 getting a much better understanding of that. I think
4 the public is much better at analyzing uncertainty.
5 We've got a whole new lexicon with diseases now. We
6 have safer sex, so I think everyone understands that
7 there isn't the cut off -- that things aren't as black
8 and white as they were 20 or 30 years ago, and I think
9 that this is reasonable information that should be
10 conveyed. The only question is how to convey it, and
11 I think it's a moving target. I think as more
12 information comes in, it can be refined in a way based
13 on data.

14 CHAIRMAN McGUIRE: Okay. John, I'd like
15 for you to give me that in a sentence.

16 DOCTOR DiGIOVANNA: To come up with a
17 sentence that I'd be finally happy with I'd have to
18 ponder it exactly.

19 I think wording about, should not become
20 pregnant while undergoing treatment or for at least
21 three years following the discontinuation of
22 treatment, and then some statement, as I said, the
23 statement -- the concept that I had originally
24 proposed was to convey that blood levels continually
25 decrease over time, and that the risk decreases over

1 time, but that this three-year period is not the magic
2 point.

3 One of the things we don't know is the
4 variation between individuals, and I don't know how to
5 put in words that without conveying some indecision.

6 DOCTOR KILPATRICK: Mr. Chairman.

7 CHAIRMAN McGUIRE: Yes, Jim.

8 DOCTOR KILPATRICK: May I put words in
9 Doctor DiGiovanna's mouth.

10 CHAIRMAN McGUIRE: Please, do.

11 DOCTOR KILPATRICK: I would feel more
12 comfortable and be more honest in saying that we
13 recommend a patient abstain from pregnancy for an
14 indefinite period, but add his point about that it's
15 well understood that the risk decreases in time. I
16 think none of us would disagree with the fact that
17 risk does decrease with time, but we simply don't
18 know, as his point is, that from individual to
19 individual what that risk is.

20 CHAIRMAN McGUIRE: And, how are we going to
21 know more in two years?

22 DOCTOR KILPATRICK: I did not mention a
23 time.

24 CHAIRMAN McGUIRE: No, no, no, I mean, two
25 years from now, or three years from now, how will the

1 Agency be better informed?

2 DOCTOR DiGIOVANNA: Can I put words back
3 into your mouth?

4 CHAIRMAN McGUIRE: This has got to stop
5 someplace.

6 DOCTOR DiGIOVANNA: Let's discuss, yes, the
7 polemics of it all. Thank you.

8 As Doctor Wilkin has suggested, I think was
9 suggesting to us, one of the areas that is an area of
10 concern is that the degree -- the extent of
11 metabolism, the parameters involved in the metabolism,
12 may vary widely across different populations. And,
13 that's uncharted territory.

14 I think information to suggest that there's
15 not a wide variation in this conversion to etretinate
16 would be relatively comforting and useful information.
17 Certainly, there is not going to be a lot of
18 information on prospective pregnancies within a very
19 long period of time.

20 Another area, if someone was willing to do
21 that, and it would obviously have to be Roche that
22 would be interested in doing that, is if a population
23 of post-treatment acitretin patients could be found
24 that have already been off the drug, and those
25 certainly may be around, that pharmacokinetics --

1 post-treatment pharmacokinetics studies could be done.
2 They could look for levels in a broader spectrum of
3 the population to get a sense, you know, is this a
4 rare event? Three years after treatment, in a patient
5 population do we find that two percent have detectable
6 etretinate, or do we find that 92 percent have
7 detectable etretinate? And, I think in that way,
8 conceivably, within a short period of time --

9 CHAIRMAN McGUIRE: For the record, are you
10 talking about plasma or tissue?

11 DOCTOR DiGIOVANNA: Well, I would be
12 talking about both, but that would remain to how one
13 would design the study.

14 But, to answer your question, how could
15 information be obtained within a two or three-year
16 period of time that might change the Agency's mind,
17 that would say that three years is a good time, or
18 three years is over kill and two years is a good time,
19 and whether that should be a definitive time, I think
20 that the information isn't there to say it, we are
21 really guessing. We are making an educated guess, and
22 we're saying etretinate, we know, I feel comfortable
23 with -- I guess it's been a natural experiment in many
24 countries where etretinate, under these guidelines of
25 suggesting that contraception not occur for two years,

1 has not resulted in a large number of teratogenic
2 outcomes, and that gives me a sense of safety, that
3 the numbers we are seeing here are probably safer than
4 we can truly evaluate on the basis of nanograms.

5 But, I think the difficulty of the
6 metabolism is one that information can be gotten over
7 a few years.

8 CHAIRMAN McGUIRE: Okay. Go right ahead.

9 DOCTOR GUINEE: Two points. I was thinking
10 that if it doesn't put the company in a poor medical
11 legal situation, that providing certain levels would
12 help to attract a prospective study cohort much faster
13 than if we didn't have something like this to attract
14 them.

15 CHAIRMAN McGUIRE: Since this is on all of
16 our minds I think, Bob, could you just give us a
17 couple of minutes and tell us what the company plans
18 to do in a prospective way in terms of measurement,
19 because I don't think that came out well this morning.

20 DOCTOR ARMSTRONG: The study that we had
21 posed to the Agency as a means of trying to do this
22 would be to take 100 women of child-bearing age, and
23 measure blood levels at the time they discontinued
24 treatment with acitretin, and then for periods at six-
25 month intervals until either there was no detectable

1 drug or five years had past, whichever one had
2 occurred first, and then use that as a way of checking
3 in the relevant population, with the advice of
4 avoiding alcohol being known to them, because one of
5 the difficulties around the world is that patients
6 started on acitretin before there was any knowledge of
7 the potential for reesterification or an
8 esterification to occur. So, that was the proposal
9 that we had made.

10 CHAIRMAN McGUIRE: Does that help the
11 committee? It doesn't help the committee.

12 DOCTOR CANTILENA: Could you not do tissue
13 levels on that, you know, similar to what's been done
14 in the past?

15 DOCTOR ARMSTRONG: The experience that
16 we've had trying to measure levels in adipose tissue
17 is that that's, first, technically much more difficult
18 and the assay's sensitivity is not as -- does not go
19 as low.

20 The second one is that there is a high
21 degree of resistance to patients to giving an adequate
22 amount, to having the biopsy required to get an
23 adequate amount of adipose tissue, because this cannot
24 be accomplished by a needle biopsy, for example. It
25 takes an open biopsy and something on the order of 30

1 grams of tissue as a minimum to be able to do an
2 assay.

3 DOCTOR CANTILENA: Well, the issue of
4 sensitivity isn't that concerning, because there's
5 usually a higher concentration in the tissue, as
6 opposed to a plasma, but I think there are some assays
7 out there that have been reported that, perhaps, you
8 know, don't require such a large sample.

9 But, the other thing that you might want to
10 consider is, you can use actually minimal sampling
11 techniques, mathematical techniques, to help you, or
12 sort of a sample towards the end of the cohort, you
13 don't have to get them every six months like you would
14 a blood plasma, and then you can actually use some,
15 you know, techniques of population pharmacokinetics to
16 actually, you know, build, if you will, a model for
17 what the generalized tissue compartment levels would
18 be.

19 So, I mean, I think there are techniques
20 that are currently used now, and that you can utilize
21 here with actually sampling the deep compartment. I
22 think that would be very valuable, to have that
23 information from that model. So, I think it is
24 possible.

25 CHAIRMAN McGUIRE: Doctor Cantilena, while

1 you have the microphone, could you tell me how you
2 would like the label to read?

3 DOCTOR CANTILENA: Yes. I guess I would
4 share the view that there's so much uncertainty, and
5 to put a hard number in the label would imply
6 certainty and knowledge on our parts, which I really
7 don't believe is currently justifiable. So, I would
8 favor, actually, the slide that Doctor Wilkin showed,
9 I haven't actually seen any of your information prior
10 to coming in with my comments this morning, but that's
11 exactly sort of the thing I was thinking about having
12 sort of reviewed the material, is to have an at least
13 and then sort of on an on-line basis, as the new
14 information comes in, just reassess that.

15 I think if -- you know, certainly your
16 pharmacokineticist would be able to assist with
17 interpreting, you know, the model and, you know, the
18 generalized -- or to help you stratify the importance
19 of the new information. So, I would favor the at
20 least three, with a clear plan to reassess as new
21 information comes in, and agree with what's been said,
22 the easier of the two types of information to obtain
23 would be pharmacokinetics, and would be comfortable,
24 you know, making new recommendations for a shorter
25 time interval, really on the pharmacokinetics, you

1 know, basis, as opposed to weighting and all the power
2 concerns that we have with, you know, the outcome
3 data, in terms of malformations.

4 CHAIRMAN McGUIRE: Ms. Cohen, how would you
5 like the label to read?

6 MS. COHEN: May I say a few editorial
7 comments. Would you mind?

8 CHAIRMAN McGUIRE: No.

9 MS. COHEN: I was just thinking that my
10 husband was a scientist at NIH for 41 years, and he
11 never published a paper unless he was certain about
12 the information, that it was correct, that it was the
13 best he could produce.

14 I'm sitting here, there's a lot of
15 information that I don't know and I haven't heard, and
16 it's hard to be a consumer member because you have to
17 speak for what you hope other people want you to say.

18 I think it's -- I don't know quite -- I
19 think it's very sad, I guess I'm disappointed that the
20 consumers don't seem to be part of this whole process,
21 and physicians and scientists look at the science, but
22 we have to look at the end. And, I don't care what
23 you put on the label, there's behavior modification,
24 people drink, people do things they shouldn't do,
25 people are frivolous, and with due respect to you

1 also, if -- didn't have enough information, there
2 wasn't enough adequate caveats on it, then go back and
3 review it.

4 But, I don't know how in good conscience
5 anybody could say, well, we are going to get the
6 information, but meanwhile we are going to do this.
7 How can you do that? I mean, if there's one child
8 that's born because of this, it's a tragedy to me, and
9 I feel sad about it, and I sit here and I torture
10 myself. There are people who need it, but what about
11 the unborn, and there's a balance in all of this.
12 And, I feel for myself, and for other consumers, if
13 some were to ask me, what did I really learn, and what
14 do I know, and what have they really studied, and I've
15 served on enough other panels besides this, I think
16 the information is inadequate.

17 And, as the consumer member, I have to tell
18 you that I'm distressed about it, and how can I
19 address that question when I don't think we have
20 adequate information?

21 I know it's a cop out, but I really feel
22 very sad sitting here about this, because there's a
23 lot of people who are going to suffer, and, in due
24 respect to you, I was in consumer protection for 15
25 years, and I can tell you some of the most intelligent

1 people I knew did some of the dumbest things.

2 So, you are giving the public more
3 information -- more credit than is due. We are trying
4 now, if I may say a little more, to educate consumers,
5 that's what is going on in the FDA, and that's what we
6 hope to do, so all of us can make an intelligent
7 decision.

8 Decisions are being made for consumers that
9 I don't think are that intelligent. So, pardon the
10 speech, and I apologize to everybody, but I am really,
11 really troubled.

12 CHAIRMAN McGUIRE: Well, I think you said
13 a lot of important things, and I'm glad you said them.

14 MS. COHEN: But, I didn't answer the
15 question, and I really can't.

16 CHAIRMAN McGUIRE: Doctor Lammer.

17 DOCTOR LAMMER: I understand what you are
18 saying, but the reality is that etretinate is on the
19 market, it's approved, and that's where things stand.

20 MS. COHEN: Does something have to be on
21 the market if you find that there are things that are
22 harmful to other people? Why does it make it carved
23 in stone if it's on the market? Why can't we
24 reconsider?

25 Life is a series of learning and changing,

1 and if something is not adequate, why can't we do
2 something different about it? That's what we are
3 about, that's what we should be about. We are a
4 deliberating body, and we have to admit sometimes we
5 make mistakes. That's better than having consumers
6 suffer because we didn't do the right thing.

7 I'm sorry again, but I need to say how I
8 feel about it.

9 CHAIRMAN MCGUIRE: You know, Susan, I had
10 an idea you were going to say some of the things you
11 said, and I'm glad you said them. I think we can't
12 decide today what to do about etretinate, we are
13 really charged with doing something about acitretin.

14 I think, Doctor Lammer, your point is on
15 target.

16 Let's see, Doctor Buntin, talk as long as
17 you like.

18 DOCTOR BUNTIN: Oh, well, I'm always to the
19 point, as you asked me.

20 My answer to the question is that I'm
21 comfortable with the Agency's labeling of "at least
22 three years," and to editorialize, I'd like to say
23 that I think it gives the practicing physician and
24 especially the dermatologist, an opportunity to have
25 a dialogue with the patient. We also must not forget

1 that a woman has a right to choose how they proceed
2 with their reproductive life, and I speak as a woman
3 doctor, as well as an advocate for patients who have
4 severe conditions.

5 I also would like to reassure people that
6 Soriatane, in my opinion, will not be a first-line
7 treatment for psoriasis. It won't be given out
8 cavalierly, and I would be surprised if anybody would
9 just hand it out, and we do have other options, but we
10 do need additional options, too.

11 CHAIRMAN MCGUIRE: Doctor Orkin?

12 DOCTOR ORKIN: I would agree with the "at
13 least three years," although, again, I would like to
14 leave out the caveat about eliminating risk with time,
15 even though it's true, I think it's just too
16 confusing.

17 CHAIRMAN MCGUIRE: Thanks, Milt.

18 Doctor Mindel?

19 DOCTOR MINDEL: The problem with putting
20 down a time like at least is that some people will not
21 interpret those words correctly, and they'll say,
22 well, my three years is up, that means -- I think
23 that's a dangerous wording to lay people, the
24 consumer.

25 I feel comfortable with the statement, the

1 period of time during which pregnancy needs to be
2 avoided after treatment is concluded has not been
3 determined.

4 CHAIRMAN McGUIRE: Okay.

5 And, Doctor Kilpatrick, you weighed in with
6 indefinite.

7 DOCTOR KILPATRICK: No, sir, I am
8 deliberately in opposition to Doctor Orkin. I do not
9 want to specify a time period, so I am with
10 indefinite, but I do think that we should add, the
11 risk decreases with time.

12 CHAIRMAN McGUIRE: Okay, you've heard the
13 opinions. Doctor DiGiovanna.

14 DOCTOR DiGIOVANNA: Too bad it's not
15 possible to put all of these concepts in somehow, that
16 to state that the risk does decrease over time, that
17 based upon the available information which is limited
18 it's recommended that a woman not become pregnant for
19 at least three years, but that the period within which
20 it is safe is not known.

21 CHAIRMAN McGUIRE: Well, I think --

22 DOCTOR DiGIOVANNA: That was a question.

23 CHAIRMAN McGUIRE: -- yes, I think we are
24 missing something very important that needs to be on
25 the label, and that is that the adverse events have

1 occurred when the pregnancy occurred concurrently with
2 drug administration. That needs to be made very
3 clear.

4 And then, we have "at least three years,"
5 and with the caveats. I think having that additional
6 information is helpful. I agree with you.

7 DOCTOR LAMMER: How was that to be worded
8 again, what are you suggesting for the wording for
9 that?

10 CHAIRMAN McGUIRE: Well, we're sort of
11 working around it, but the concept is that, I feel the
12 consensus is that pregnancy should be avoided for at
13 least three years. We don't know how long it should
14 be avoided.

15 What we do know for sure is that if the
16 drug is administered during pregnancy, there will very
17 likely be adverse events. We know that.

18 DOCTOR LAMMER: I guess that's the sentence
19 I'm asking you to be more clear about. You are going
20 to use the 25 percent risk that we saw here today
21 explicitly stated that way?

22 CHAIRMAN McGUIRE: Well, you know, the
23 problem -- we could, that will be an Agency decision,
24 but the problem I have is that the sample sizes are so
25 small it's hard to leverage yourself out there very

1 far on those numbers. And so, you may be pumping up
2 the risk artificially, or you may be diminishing them.
3 I really think we just need more data.

4 But, at the same time, I think we should
5 emphasize that concurrent administration with
6 pregnancy is clearly going to result in embryopathy.

7 DOCTOR LAMMER: That's not what the data
8 shows. That's inconsistent with what the data showed,
9 which was that 25 percent of the pregnancies in which
10 the drug was used during pregnancy resulted in a baby
11 with a malformation.

12 CHAIRMAN McGUIRE: Right.

13 DOCTOR LAMMER: So, to say that all of them
14 are abnormal isn't consistent.

15 CHAIRMAN McGUIRE: Oh, if I said all, I
16 didn't mean that.

17 DOCTOR LAMMER: Or, something to that
18 effect. I think it has to be worded carefully.

19 CHAIRMAN McGUIRE: Well, Doctor Lammer, I
20 think the risks during pregnancy are such that you
21 wouldn't undertake those risks.

22 DOCTOR LAMMER: Really? Well, we talk to
23 women all the time who have had a child with a
24 recessively inherited condition, who have a 25 percent
25 risk of having a recurrence, and to some families 25

1 percent in that situation is an acceptable risk to
2 them, for other families that risk figure is not
3 acceptable.

4 So, I think it's better to just lay out the
5 data, what the numbers are, for people, you know, what
6 the numbers are that was presented by Roche today. I
7 mean, the drug is clearly contraindicated for use
8 during pregnancy, I'm assuming. Am I right about
9 that? It's already going to say that it's
10 contraindicated for use during pregnancy. I think it
11 is inaccurate to say something to the effect that
12 every fetus is going to be affected in some way.

13 CHAIRMAN McGUIRE: I hope I didn't say
14 that.

15 DOCTOR LAMMER: Okay.

16 CHAIRMAN McGUIRE: Doctor Wilkin, are you
17 hearing a consensus?

18 DOCTOR WILKIN: Well, I think that we're
19 getting a message, but I did want to just make one
20 clarification. At the conclusion of Doctor
21 Cantilena's comments, you indicated more PK data, were
22 you thinking of just the traditional classical
23 pharmacokinetics parameters, or are you also thinking
24 of the metabolic studies in that same -- under that
25 same rubric?

1 DOCTOR CANTILENA: Yes, I did not intend to
2 limit it to just one time.

3 CHAIRMAN McGUIRE: John, do we have further
4 business?

5 DOCTOR WILKIN: Well, we very much
6 appreciate the committee thinking about this issue,
7 and we appreciate the sponsor presenting their
8 material, and being available for answering questions.

9 CHAIRMAN McGUIRE: And, I would like to
10 express my thanks for people who took a couple of days
11 out of their lives and came from the West Coast to
12 give us some advice. Thank you.

13 We are adjourned.

14 (Whereupon, the meeting was concluded at
15 3:49 p.m.)

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