Accutane.

In closing, I feel this is not a new problem. Two, I think the Advisory Panel made up of experts in our field have carefully scrutinized the use of the drug earlier, and I am sure they will continue to carefully scrutinize it.

Three, our specialists in dermatology are responsible individuals, as witnessed by a gradual decrease in the number of pregnancies--although I will agree that the goal is to have zero pregnancies. We cannot deny our patients a cure. The alternate use of illegally obtained material on a readily available substitute such as retinol without proper supervision will likely lead to more problems instead of less.

I thank you for the opportunity to appear before you.

DR. DEL VECCHIO: Thank you, Dr. Shalita and Dr. Strauss.

We have now discussed why Accutane is essential in the treatment of severe recalcitrant cystic acne. The next question is: How many patients are there with severe recalcitrant cystic acne? How many patients qualify for Accutane therapy? How many of them are fertile women?

A discussion of the population in question is

critical to discuss the options that we will be going through this afternoon.

In order to show you where we differ from Dr. Graham and his associates and where there are similarities, I am going to present this brief comparison. I should note that the numbers referred to in the memo column on the left referred to Dr. Graham's memo, and they are not updated for the numbers that were presented here this morning. The numbers on the right are the numbers I will be showing you shortly.

Basically in terms of order of magnitude, based on the same types of surveys, NDTI, NPDS, we are in fact not very far apart in terms of women of child-bearing age who have been treated with Accutane. As a matter of fact, our number at the end of 1986, the same as this, is 366,000, right in this range.

As far as annual exposure, their calculations are 65- to 95,000; ours are 61- to 100,000; theirs should be 116,000, and I'll talk about that later. The big place that we differ--and this number changed this morning--is now instead of less than 3 percent, is now 7 percent. That is, that 93 percent of the use of Accutane is inappropriate. We in fact will be talking about numbers that say that approximately 98.5 percent of the use of the drug is appropriate according to

dermatologist surveys.

In order to show you where some of the differences come from, I have to refer back to a summary chart that comes from Dr. Graham's original memo. These numbers again have now changed this morning. This number of the population size is now 450,000 based on 1984 data. Based on 1987 data, in fact it is well over 500,000 using the same study.

This is then factored down by a series of factors to arrive at the original figure of less than 1000 female patients who require Accutane. The first factor was how many of them are severe, and originally in the paper it was 50- to 75 percent. As of this morning, it is down to 50 percent, and perhaps even less than that. As you just heard Dr. Strauss say, it may be much closer to 100 percent.

In any event, that particular factor is based on no scientific data, no evidence of any kind. It is purely a guess. The next major factor, however, is an important one. That is, the 5 to 1 or 15 percent ratio of women to males.

I am not sure why there is a bias inherent in studies of patients reporting to a physician's office, as Dr. Graham stated this morning. As a matter of fact, I think there may be a bigger bias present in simply

doing population studies regardless of who comes into the office. The FDA reviews and approves drugs for use by physicians in their offices in patients who arrive in the office asking for help.

It seems to us that that is the appropriate place to measure what the incidence is of the disease that is being treated. In any event, even looking at the studies that Dr. Graham and his group have reviewed, that ratio simply doesn't hold up.

Without going into great detail, let me just tell you that the ratio is based on two United Kingdom population studies which are misquoted on data and contain conclusions directly contradictory to Dr. Graham's conclusions. They are based on three treatment studies which were biased against entry by women into the studies on the basis of various selection and exclusion criteria.

They are based on that single 15-year-old population study which in fact showed that more women sought treatment than men, even though it did show a 5.5 to 1 ratio of men to women in the population. It also showed a 1.25 to 1 ratio of women to men presenting to the dermatologist for care of their acne. We will show in fact that this percent is 50-50 in terms of patients who come into the doctor's office.

The unresponsiveness, the Graham memo and Dr. Graham this morning stated that only 5 to 15 percent of patients should be unresponsive to other therapy and therefore recalcitrant and fit into the diagnosis that is applicable to Accutane.

I will not go into detail on the basis for this except to say that the same types of errors occur in this analysis as in the first, and there is no evidence whatsoever presented in the paper to support the presumption that sequential therapy of a variety of treatments will result in a very small group of patients who will not respond to one or another of the treatments, and to emphasize what Dr. Strauss said earlier, every single one of the alternative treatments that is mentioned in Dr. Graham's memo is not approved for us in acne, with the exception of tetracyclines, which are only approved as adjunctive use for severe acne.

In addition to that, although mention is made of the memo, that in fact the pregnancy category, the safety of the drugs is not well established in pregnancy, no further mention is made of the implications of that; that these drugs are not labeled anywhere near as stringently as Accutane.

And finally, another important factor is that

of the new onset--that is, the incidence. Again, that changed somewhat this morning. Dr. Graham is now saying that the average duration of cystic acne is 8 to 9 years. It was 10 years in the memo, and therefore the prevalence is factored down by 10 percent to get the final figure.

That particular 10-year duration of cystic acne is based on two studies of cystic acne. Those studies give a duration of 8 to 9 years for acne in any form. Neither one of those studies makes any statement about the duration of cystic acne. Both of them simply state that acne in any form was present for 8 to 9 years in those patients.

So again we have taken an erroneous reading of the material and built it into this figure. Now again this figure is now 4300. We reject that figure, too. We don't believe that is anywhere close to the appropriate number of women who need to receive Accutane.

I am going to present some market surveys. Market surveys are always open to questions of precision, and also questions of bias. I anticipate questions and comments about our market survey, so let me precondition this by saying these are presented as orders of magnitude. We are not presenting them as

precise population figures.

However, having said that, we believe that these surveys are reasonably valid for these reasons:

First of all, they are not privately sponsored surveys; they are public; they are available. The FDA uses them. They are the industry standards for making decisions. They are used in marketing decisions throughout the industry, not just by Roche. And the studies that we are using are remarkably consistent across a five-year period with different physicians and different pharmacies. The consistency we believe as to the validity of the studies.

This first one, and I won't go through all the details of this--this is from NDTI, the same studies quoted by Dr. Graham--this is cystic acne as defined by office-based physicians, dermatologists, and other physicians. They are not given a definition. This is their own definition of cystic acne. I just wanted you to see a few points here.

Total visits for cystic acne have been basically level at about 1 million visits from 1983 through 1987, and basically the ratio of male to female which was somewhat higher has now dropped to 1 to 1. I think we have some question about whether or not that drop has something to do with the marketing of Accutane,

but we really don't know that.

The first visits, if you will, the incidence of new patients at least in the doctor's office, is also basically level at approximately 250,000, and again the incidence basically is 1 to 1. These numbers come from market measures and other publicly available surveys. I should say this survey study is done with 200 dermatologists every year who were asked the same series of questions every year, and they are rotated so that over a five-year period we are dealing with approximately 1000 dermatologists. Again you will see the consistency in the kinds of reports that they give us.

Total acne visits from that period of time seemed to be dropping. They seem to have peaked in 1984 and 1985, and they have now dropped to around 8 million visits. Of those, there are approximately 1.5 million new acne patients. When asked what percentage of the new patients were Grade IV patients, Grade IV by their own definition--no definitions were given; as was said earlier, you can't really define this; there are no standards--is approximately 156,000 new Grade IV patients seen by physicians, by dermatologists, in 1987. The percentages from the previous slide are approximately 50 percent. We are talking about

approximately 77,000-78,000 Grade IV women's first visits to a dermatologist for that acne.

I would like to go on now to another data service, and that is PDS, Pharmaceutical Data Services. That measures patients by actual prescriptions filled. Now whatever we may say about how many visits there are to the doctors' offices, how many prescriptions are written by NDTI, these in fact are the actual patients who buy prescriptions. These are the prescriptions that are filled and walk about of the drug store. We do not know whether they take the Accutane or not, but these in fact are the prescriptions.

The totals for Accutane, the total patients peaked from 1983 to 1985, and has now been dropping by about 10 percent per year for the last two years. New patients, first visits, not otherwise duplicated in the total--that is, patients who have never been in before in this period of time, the previous period of time--again peaked in 1983 and is approximately one-half what it was in 1983 in 1987. Those are total patients.

How many of them are women? These are the new patients from the previous slide. The PDS gives us a percentage of women. In 1987 it was 51 percent. That turns out to be estimated at 80,000--and I have to say these are estimates. These are not precise data. They

are estimates based on raw data given to us by PDS. PDS does not make these up. We make them up from the raw data, and we put that disclaimer on it to begin with.

But you see an interesting trend here from 1983 to 1987. The number of new female patients has dropped from 141,000 to 80,000. Among those new female patients, let's look at the number who are age 12 to 44. That age bracket is the closest that PDS comes in terms of the age brackets to the age that we are talking about. Again, total new patients, the percent of those that are females in the age bracket 12 to 44: 61,000 in 1987; a peak of 116,000 in 1983. In 1987, approximately one-half the number of women of child-bearing age were treated with Accutane as were treated in 1983 in terms of new patients.

I would submit to you that far from increased and indiscriminate use, that these data show that in fact prescriptions have decreased sharply since the first reports of congenital malformations in 1983, and the information that went out in 1983 and 1984. I think this is a very clear indication of two possible reasons here.

One is the congential malformations, and the increased care with which dermatologists and other physicians are prescribing this drug in this age group;

and second, perhaps this says something about the efficacy of Accutane and that we may be approaching whatever that baseline incidence is.

Just to put this figure into perspective, just as Dr. Strauss put the figure into perspective before, that if Dr. Graham's figures were correct, that the average dermatologist would see less than one patient per year who is a woman in this age group who requires Accutane. To put that figure in perspective, it would mean that the average dermatologist would see one new female patient per month who requires Accutane therapy.

I would ask those of you who are dermatologists on the Advisory Committee and in the audience if that does not in fact reflect what would seem to be a reasonable approach to the use of this particular product, and that it is not any more rare than that.

I am not standing here claiming that every one of those 61,000 patients met the exact criteria for severe recalcitrant cystic acne, but the next slide is in fact an extension of that previous survey. This part of it is private. This is a Roche-sponsored part of the market measure survey, so I will state that up front that it is not available publicly. We are giving you the data. It is in our response to Dr. Graham's memo

over the five-year period.

Those same dermatologists were asked to think of the last patient that they treated with Accutane who completed a full course of therapy, and they were asked to grade that patient by Grades I, II, III, Grade III to Grade IV, whatever that is. I'm not really sure. It is something in between the two. And Grade IV. I am not going to argue about which of these grades fit into the classification of Accutane, but consistently over five years between Grades III and IV and in between, this is 98.5 percent of the dermatologists's report that their last patient was in one of these three categories.

Now even if you wish to say that that, for whatever reason, does not fit the criterion for treatment with Accutane, that simply represents 13 percent. Our feeling is that, as Dr. Shalita said, the practicing physician certainly is not practicing inappropriately if he chooses to treat that patient.

Again, I am not saying that 98.5 percent of all Accutane prescriptions are directly related to the package insert diagnosis, but we certainly are not dealing with 93 percent in the other direction.

I might add, in this particular study the physicians and dermatologists were also asked, before you treated it with Accutane what was the patient

treated with? Over 90 percent of the patients were treated with systemic antibiotics.

The group health data from Dr. Jick, which Dr. Graham also has in one of the studies he used to validate his data, in fact shows exactly the same thing: that over 90 percent of the patients in Puget Sound who received Accutane were treated with systemic antibiotics before they received Accutane.

We submit that in fact dermatologists and other physicians are practicing appropriately by using the appropriate systemic antibiotics before they move to Accutane.

Just to summarize that portion, according to dermatology office visits and actual prescriptions, there are approximately 250,000 new cystic acne patients per year. There were approximately 156,000 of those patients in 1987 who were new patients fitting into Grade IV. The male to female ratio is 1 to 1. Approximately 60,000 new female Accutane patients in the age group of 12 to 44--and that number is steadily declining and not increasing.

Again, let me repeat the difference in our data. If Dr. Graham's number is anywhere near correct, we are talking about one new female patient in that age bracket per dermatologist per year. If our figures are

nearly correct, we are talking about one new female patient who requires Accutane per dermatologist per month.

We believe that our data are correct. We also believe that this is a very important issue, as I stated earlier, and that the issue itself and the discussion of that issue is poorly served by clouding it with the inappropriate use of data and statistics.

I would like to go on to make a couple of comments about the Michigan Medicaid study--and I promise you I will not go into great detail on this.

We have also calculated rates for the Michigan Medicaid study. According to our data, all the patients served, the average number of patients served per year was in fact over 400,000 patients, not the 269,000 quoted by Dr. Graham. Therefore, there are differences in our rates. But basically if you will look at the rates that we have obtained, suspected Accutane--and we have serious questions about how exposure was determined, and I think Dr. Stern has raised some of those questions already--in terms of pregnancy rates in patients suspected of receiving Accutane, the pregnancy rate is one-half that of the Michigan Medicaid patients in general, and one-half that of the U.S. population.

The live birth rate is one-fifth that of

Michigan Medicaid patients in total, and approximately the same ratio in the U.S. population.

The induced abortion rate in patients who are suspected, 4000 women suspected of having received Accutane, is the same in that group as it is in Michigan Medicaid as a whole and in the U.S. population at large.

Now it is correct that when you take that figure per 1000 pregnancies, that in fact it is doubled. We are talking about per 1000 women. The bottom line of this means that a single woman in the Michigan Medicaid system, whether she does or does not take Accutane, is no more likely to suffer an induced abortion in any one year. And in terms of spontaneous abortions, again suspected Accutane, all Michigan Medicaid patients, considerably less than the U.S. population, there's something wrong with that. That ought to be higher, as far as we're concerned, in terms of the Medicaid population. I think it is one of the reasons why in fact this is not extrapolatable.

All of this, however, I think can be read to say that perhaps the Accutane intervention is working. That pregnancy rate, even if we accept all of these as being teratogenic exposures, and we do not, the pregnancy rate is at least half that in the rest of the population. It ought to be lower than that.

The abortion rate is double in patients who become pregnant. I think that is reflective of exactly what the warnings are, and what the suggestions are in the Accutane labeling.

By the way, I might add that we have another reference that says that this rate for Michigan Medicaid in general is actually 51 percent, and that is in our response paper. I would refer anyone here who wishes to go into great detail on this to our response paper to Dr. Graham's original preliminary memo.

I am not going to go through each of these. These we believe are the major flaws, or most of the major flaws in using the Michigan Medicaid data base to project to the national population, and they have to do with things like drug exposure versus drug purchase, which I think was asked earlier this morning; how did they get into Medicaid? How do you determine exposed pregnancies?

We totally disagree with 120-day and 270-day criteria. The failure to take into account a large number of confounding variables--and those are just some of them. The sample size simply is insufficient to make that kind of determination. The trend over time is not as presented by Dr. Graham on his own slide. In the first 28 months of the 5-year study, or the 4.5-year

study, about two-thirds of the pregnancies occurred; and in the last 24 months, about one-third occurred.

And finally, of course, projection--that is, what are the characteristics of Medicaid patients that allow us to project to the national population. I do not have enough time to go into all of these fallacies. As I said, our response paper on pages 43 through 57 goes into much greater detail, and we would certainly request an objective review of both Dr. Graham's memo and our response by any interested third-party, including the Agency, in terms of whether or not what we are saying is correct, and whether or not these data can be supported.

I might add, Dr. Graham mentioned this morning that there are 50 states that have Medicaid systems. That is correct. I might also add that 24 states in this country have reported no congenital malformations. Six or seven states have reported no pregnancies. Obviously, depending on which state you choose to take, you come out with some very different conclusions.

I don't mean to minimize this in any way. We have never tried to minimize the issue. The issue is a major issue. We simply cannot abide by the use of these kinds of data to make not only conclusions, but recommendations which are spread throughout the country

via the media, which is certainly nonsubstantiated and nonsupportable.

I just have one more comment to make in regard to Dr. Graham's presentation and memo, and I will leave that comment to the memo itself. And that says that: Although questions may be raised regarding a methodologic approach to the Medicaid study described in this document, the occurrence of a two-fold increase in induced abortion and the possibility of two birth defects plus possibly three other stillbirths or early post-natal deaths among deliveries of women suspected of first trimester Accutane exposures supports the validity of the method and the data.

Loosely translated, to us what this statement says is that although there are questions regarding the methodology in analyzing this particular study, the results were what we expected to obtain, and therefore that supports the method. In other words, the results validated the hypothesis and therefore the method is correct.

We would simply submit that that is not the kind of statistical philosophy that is acceptable to the FDA nor to us, and I think it calls into question the bias of the entire analysis of the Michigan Medicaid system.

I would now like to introduce Dr. James LaBraico, our Director of Drug Safety, who will discuss our data on teratogenicity, on overall ADEs, and on the adequacy of reporting.

Adverse Experience Data Presentation by Dr. Hames H. LaBraico, M.D., Senior Director, Drug Safety

DR. LaBRAICO: Good morning.

I work in the Department of Drug Safety, and I would like to emphasize that I will present the information from the spontaneous reporting system as we have gathered together. I do not intend to get into a number-debating issue, because I think the problem is real and I put the data together in ways which I think will give us clues and some guidelines as to how we might better deal with the problem. So if I may have the first slide.

[Hereafter, slides are shown.]

This includes 363 cases of pregnancy that have been reported to us since the marketing of Accutane in September 1983. The top line shows the number of congenital malformations, the peak--and this is by the year of exposure--the peak year being in 1983.

The second line shows the number of spontaneous abortions. This differs from Dr. Graham's

number, and I won't get into this issue unless somebody asks the question. In regard to the number of elective abortions on the next line, we have 191 reports. I might add that of the congenital anomalies, 13 have been reported by dermatologists, and in the elective abortion area 120.

There have been 60 normal births. We still have 10 cases that are active in follow-up, although these are coming to some resolution. In the "continuing," I know that there are three normal babies that have been born. And then, "cases lost to follow-up." We therefore look at the total reports in each year as they come into the company, the peak year being 1983. There was some decline and a relative plateau over the last several years.

This pregnancy rate refers to the number of pregnancies in the population that Dr. Del Vecchio alluded to earlier as far as the number of patients that have actually been treated with Accutane.

I would like to deal just a little bit with the spontaneous reporting system. I think we all have to recognize that if it weren't for that, we wouldn't be here today. Also, what about Accutane as one looks at it from the standpoint of reporting and the awareness of reporting?

People have talked about a cycle of reporting when a product is on the market two or three years, that there is a drop-off in reporting. Certainly this has not happened with Accutane. It has maintained a steady level of reporting over the past several years. We have estimated that in this reporting period of time we have heard from about 3000 dermatologists. So I think that, while it is not perfect, I think with this particular product and with the community that we are involved with, it has proven to be a good system and it has kept us aware of what has been going on with this product over the past several years.

In regard to the issue of congenital anomalies, we get constant ADE reports. That has maintained a significant plateau level. There has been a fall-off in the reports of pregnancies. Since this has been constant, we might be able to assume that there is some reality to the fact that the pregnancy reports have dropped off.

There have been reports from Roche, from the FDA to report, the public media has been involved even in the past before this recent weekend; it's too early to tell yet, but I can tell you that through yesterday we did not receive a single pregnancy report. We will continue to monitor this in light of all the recent

publicity.

I think the nature of the abnormality, involvement of other specialists in the field, there are state and national registries. We know that in New Jersey last year a request in the middle of the year came out on this issue, and as of a few weeks ago that had not generated any new reports.

There is Dr. Stern's program. He recently published his results on this program in March, and 11 percent of the reports in that group were on pregnancies. We are involved in post-marketing studies. The study that Dr. Graham alluded to--I might add on this point here, on the pregnancy cases, these are suspect and have never been confirmed that there was true exposure.

Questions have been asked regarding the physicians involved. This information is, where we have the information, 87 percent--and I say prescribing physician; they are not always necesarily the reporting physician, but we have been able to clearly identify the prescribing physician.

In this area where it says "unknown," these cases were not initially reported by dermatologists. It will sometimes be alluded to the fact that there is a treating dermatologist, but unless we can specifically

confirm that to be true, we have not indicated that. And I usually mean that by "name."

The diagnosis that's been involved in these patients over the years, cystic acne has been the diagnosis. These are diagnoses given to us by the reporting physician: 68 percent cystic acne. In the acne group where there are 50 cases, I might add that 80 percent of those diagnoses were not by dermatologists but by other reporting physicians such as obstetrics and gynecology, geneticist, and others in that area. There was one accidental ingestion. This was a patient in a clinical trial where the mother happened to take a capsule by mistake.

I would like to take a look at what we have gleaned from birth control in these patients. This is a small number, but I think it is worth pointing out: women who feel they're infertile. I think this has to be evaluated very carefully when these histories are given and probably not taken just at face value.

The other area is 50 percent of the women indicate no birth control. This was a question that was raised before regarding this issue. Then these percentages over here refer not obviously to the total, but to the total number of pregnancy cases, and there have been reports of oral contraceptive failues,

although we do know in some of these cases that there appears to be patient failure, maybe not method failure.

This is an age breakdown of patients who were pregnant before starting Accutane, about one-third, and they fall through all age groups. While there are teenage pregnancies, it is not purely a teenage problem.

I put this slide up because I think it shows some interesting information regarding the timing of when the drug was taken. We see several significant numbers of the women who were at about two weeks or less in their pregnancy before the drug was prescribed who by historical means obviously would not know at the time that they were pregnant because they had not gone through another cycle. You could actually extend that to three weeks. And a similar type of thing occurs when one looks at exposure afterwards.

This is a breakdown by age because we wanted to demonstrate that the age is fairly spread across a variety of age areas. It is about 70 percent that are above the teenage category, but indeed there is a problem in that group that has to be addressed.

Thank you. That is basically the data I wanted to present. I can answer questions that you might have at the moment.

DR. DEL VECCHIO: Just to summarize and give

you our conclusions for this morning's presentation:

First, Accutane is a medically essential drug for a significant portion of the population.

Second, there is decreasing use in women of child-bearing age.

Third, it is being properly prescribed in the majority of cases.

And fourth, our ADR reporting system captures most of the congenital malformations.

We thank you for your attention. We will be presenting our proposals to deal with the issues involved here this afternoon, and we will welcome any questions or comments at this time.

DR. BERGFELD: Thank you, Dr. Del Vecchio. I think we will move on to the next presenter, and then discuss these two presentations as one.

We have next Dr. Joel Kuritsky, Chief of the Epidemiology Branch, Office of Epidemiology and Biostatistics, FDA.

Review of the Data by Dr. Joel Kuritsky, M.D.
Chief, Epidemiology Branch, Office of Epidemiology and Biostatistics
Food and Drug Administration

DR. KURITSKY: Thank you.

The presentation by Dr. Graham this morning

was very technical, and I wanted to address three points for your deliberations.

DR. BERGFELD: Would you speak into the microphone.

DR. KURITSKY: Yes. I want to address three points for your deliberations. I also need to comment on some of the data presented by the company representatives.

I think it is important for the committee to understand surveillance systems. I just want to touch on that. The surveillance system that we use at the FDA is primarily a passive surveillance system. That is, we obtain reports without stimulating the reporter.

With the Accutane issue, with the variety of articles, there probably has been what we call stimulation and that results in a system that we in epidemiology call a passive stimulated system. The one system that is in place currently that uses passive stimulated data collection methods, and has used it for years, is the CDC system in Atlanta on adverse reactions after immunizations.

I think it is very important to understand that even in the light, for example, of what Dr. Graham showed this morning, in the light of SDS after DPT, under the best of circumstances passive stimuated

systems rarely get above 20 percent of the reports that one would expect, and that is almost universally true.

In another example where the CDC went into Pierce County, Washington, looking for reports of Hepatitis B, which is a legally reportable disease, and in Pierce County they had a stimulated system, when they actively surveyed for disease through hospital based reports and laboratory based reports, they were able to increase reports of Hepatitis B by 50 percent and non-A/non-B by over 100 percent.

So I think it is absolutely essential and clear to understand that the number of birth defects for reports that we are getting probably represent only a fraction of the total number out there. I don't think anybody who has been involved in surveillance would either at the primary level or at the state, or at the secondary level at the CDC or the FDA, would deny that.

The second point I want to address is the validity of population-based studies for determining the prevalence and incidence of disease. We don't at the FDA use NDTI to look at prevalence and incidence rates. There is danger in doing that, because persons who go to the doctor for a problem may in fact not have that problem. I just want to show one overhead which demonstrates the problem within ETI and coding that is

necessary.

Do you have the overhead over there? You have to remember that in NDTI the physician is using a code after he sees a patient, and that is an ICD-9 code. If David doesn't have it [the overhead], the bottom line is we tried to replicate the Roche response to us using the ICD-9 diagnosis code for cystic acne, and we came up with numbers that were a quarter--basically a quarter of the numbers that the company came up with.

What this suggests to me that there are problems with the coding, and there is a great deal of variability in the coding, and one has to be very careful how they use these ICD-9 codes. There is misclassification that occurs at the coding side where somebody in fact can code for cystic acne and the patient could have acne, or somebody could code for acne and the patient could have cystic acne.

So our numbers don't reflect the Roche numbers, and I suspect that they lumped a variety of other acne codes in there to come up with their figures which are about three-fold what we have, but I don't have verification of that.

The second problem with nonpopulation-based data, with survey data are the essential problems in epidemiology. They are recall bias, interviewer bias,

and sampling bias. Market Survey's data is a survey that asks the physician: How many patients with cystic acne did you see?

If one wants to use that data to extrapolate to prevalence and incidence of disease, one needs to validate that what was reported by the physician was actually seen. That is why I think that most epidemiologists would agree that population-based data, especially the NHANES data, is likely to be the most reliable data on which to base incidence and prevalence data.

Finally, I just want to mention the issue of use of the product. The use of the product in the United States is greater than the use of the product in, to our knowledge, in countries where we have good data, population-based data in women of childbearing age, and that is primarily in Sweden, the use in Sweden and Great Britain appears to be a fraction of what the use is in the United States, and that use is a reflection of the restricted nature of giving the product but also cannot be used to reflect prevalence in incidence of disease. I think the key point here is to remember that population-based data, especially the NHANES data which was examination-based, and the examination basis of it prevents a bias in either

talking to the patient or talking to the physician which subscribes as most accurate, and the fact that that population-based data was repeated in other studies in Great Britain adds more credibility to it.

Finally, I need to say that internally we debated long and hard about the data, and looked very hard at the Medicaid data. The fact that it was replicated, courses of it replicated, two other data bases, Florida Medicaid and Group Health Cooperative in Puget Sound, gives it, in an epidemiologic sense, more validity, and I think, we feel fairly strongly that that data is valid and unbiased in most ways looking at the number of pregnancy exposures and the outcome.

In sum, I think I conclude, along with my cohorts that the product based on population-based data, the least biased of all data, is overused for its intended indication. There have been pregnancy exposures in three different locations that we know of in the United States, three different data bases, population-based data bases, and I suspect there are pregnancy exposures in many other data bases, and that birth defects continue to be reported, and one cannot use the reports of birth defects as a numerator and stick it over a denominator of use, and reach any conclusion about the rate of birth defects that are

occurring in the United States, it just cannot be done, and I would attest that reporting in the United States, with any surveillance system, unless it is extremely active, laboratory-based, autopsy based, is underreported. In almost all systems that I have looked at the CDC, even with required reporting, we are only getting at best, 20 to 40 percent of the reports.

So I just wanted to make those points clear for the Committee's deliberations.

DR. BERGFELD: Doctor, you also will be around for questions, will you not?

DR. KURITSKY: Yes.

DR. BERGFELD: Then, I would like to move to Dr. Thomas Jansen who is the current President of the American Academy of Dermatology who would like to present his statement.

DR. JANSEN: Dr. Bergfeld, I appreciate being here to give this statement on behalf of the American Academy of Dermatology. I am Tom Jansen, I am a physician, a dermatologist with 32 years of private practice experience in Little Rock, Arkansas. As President of the American Academy of Dermatology, I represent the 7,000 physician members of this group. As a clinician in Little Rock, I know I represent the patients that I have treated with Accutane in the past

six years, and I trust that I will also represent those future patients with severe cystic acne who would need this drug.

The Academy of Dermatology is the leading society for the promulgation of post-graduate education through our meetings and scientific publications as well as other educational programs. We dermatologists recognize that severe cystic acne is a disease that can produce profound permanent scarring of the face, neck, chest and back that was so well illustrated by the clinical slides from Dr. Shalita and Dr. Strauss. Until the introduction of Accutane, no predictably effective treatment for this disease really existed. In addition, cystic acne is not a self-limited process that magically disappears at the conclusion of adolescence. To the contrary, it can persist for many, many years, even during the course of most adult life. Although the treatments were available for this disease before isotretinoin, the response to systemically administered antibiotics, sulfanomides, sulfones, anti-inflammatory agents, including corticosteroids, hormones and high doses of Vitamin A, in the range of 100,000 to 200,000 units a day, were unpredictable, incomplete, and temporary at best. Even given in sequential fashion, or in combination.

Many of these drugs were given for months and years, and also had significant side effects. A number of them were contraindicated during pregnancy, and the question still exists about whether some of them may have reduced the effectiveness of birth control pills. Topical therapy is ineffective in most instances of cystic acne. Dermatologists know that there are no alternate treatments for this severe disease that offers the same cure and improvement. In fact, we could never speak in terms of cure until the introduction of this drug but rather effective treatment was measured as 50 percent improvement.

There are a great number of drugs that should not be given during pregnancy, and Accutane is among them. The Academy has stressed this danger, along with the manufacturer, since its approval in 1982. In spite of these concerns, we who are the experts in this disease, its natural history, and the ineffectiveness of alternate treatments concluded that the benefit-risk ratio justifies its present and continued use with appropriate warnings and protection against pregnancy during therapy, and it should be noted that these effects disappear shortly after the drug is discontinued.

Withdrawal of isotretinoin would again

obligate us to see patients more frequently, to see them over a longer period of time, to incise and drain the lesions that were so vividly demonstrated in the slides that you saw. This would have to be repeated from time to time, and these incisions are then followed by an injection of a steroid into the lesion itself.

The Academy has had a long history of effective, active efforts toward the prevention of disease and protection of our patients from disease. Our most recent and visible activity is perhaps illustrated by our National Melanoma Skin Cancer Protection Program, which will be held again this May as it has been held the last few years. This voluntary effort by the members of the Academy of Dermatology certainly should underscore the desires that we have to protect our patients and to secure their welfare. The Academy is sensitive to the issues being raised at this hearing. The Academy pledges its resources in educating our members to the policies that are an outcome of these hearings, and we make a strong plea that this drug should be available to help our patients.

Again, on behalf of the membership of the Academy, I would like to thank the Committee for

permitting me to appear, and I, too, will be available during the course of the day should there be any further questions. Thank you.

DR. BERGFELD: Thank you, Dr. Jansen. Next on our agenda is Dr. Sidney Wolfe who is in the Health Research Group, Washington, D.C. Dr. Wolfe, are you here?

DR. WOLFE: The bulk of our presentation this morning will be given by Lynn Silver who is at my right who is a pediatrician, and a public health expert who is on our staff, and Bill Schultz, to her right, who has been, for the last 10 years, one of the lawyers in Policies and Litigation Group working particularly on problems with prescription drugs, the need for stronger warning labels, the need for bans when the occasion arises and so forth.

Before they take over, I just want to spend a minute or two commenting on the background of this and on some of the things that have been said this morning. About a year after this drug came on the market, and after I had received notices through the mail of birth defects occurring as a result of its use, we petitioned the Food and Drug Administration in September of 1983 to do a number of things by way of increasing the warnings, educating physicians,

educating patients, so that one could retain the benefits of this drug, which I do not think anyone disputes, but at the same time, significantly reduce the risk. One of the things we focused most heavily on was the absence at that time in the labelling for this drug of a required pregnancy test on a woman of childbearing age as a precondition for the drug being prescribed.

We did not know, at the time of our petition, which eventually succeeded in a pregnancy test requirement being added to the labelling, what we did not know was that prior to the time the drug was approved, during the last stages of clinical trials, there had been a pregnancy test required as a precondition for women of childbearing age before they got the drug on an experimental basis. I would have to describe that the dropping of this requirement for a pregnancy test by the company, Roche, was reckless, and it sort of helped to set the tone for the fact that this drug, although everyone said it causes birth defects in animals, and you should not use it for pregnant women, you did not have this later to appear issue of doing a pregnancy test. I think it raises the level of seriousness, and I have never yet heard an explanation from the company as to why this was

dropped. I have heard some silly explanations like there are a lot of things we do during clinical trials that we do not do during the marketing.

It is inexcusable that this drug came on the market without a requirement for a pregnancy test, and I would add it should be a repeated requirement. Since the drug came on the market, the company has sold over $300 million worth of the drug worldwide, and in this country alone, if one just looks at the reported cases, there are 66 cases of severe birth defects. Whether the number is 66 or 166 or 866, it is too many. A number of the parents of these unfortunate children, the ones who lived, were invited to come to this hearing, and I understand they by and large did not want to, it was too painful an experience for them to go through. I think what is clear is that the alleged radical proposals, both Roche has described its future proposal as radical, and Dr. Tabor described, I think correctly, as some of the things that the FDA did in 1982 or 1983 as radical. None of them were radical enough. We have a proposal which we will offer. I would not call it radical. I would call it sensible, and I will turn it over to Lynn.

DR. BERGFELD: Excuse me, before you begin, can you give us a time period that you plan to make

this presentation in?

DR. WOLFE: Mine is over.

DR. BERGFELD: I know, but you have two other people.

DR. WOLFE: Probably 15 minutes or so at the most.

DR. BERGFELD: All right. I would have to say that we must restrict you to a maximum 15 minutes.

DR. WOLFE: Okay. Bill just has a minute or so of comments, and Lynn has less than that. Thanks.

DR. SILVER: The Committee is charged with advising the Food and Drug Administration on one of the drugs that has the highest risks of severe birth defects of any drug marketed in the United States. We want to point this out because this is not common. There are not 50 drugs out there that are like Accutane. It is a rate condition. Accutane is one of the most powerful teratogenic drugs known, causing specific severe defects in up to one-quarter of pregnancies. These defects have been identified as due to the drug as Roche agrees.

As Sidney pointed out, we do feel that the number of defects that have occurred since 1982 were increased by the fact that this drug was placed on the market without a requirement for pregnancy tests

despite the evidence of its teratogenicity. We also feel that the number of birth defects was increased by the failure to effectively restrict the marketing of this drug from the very time that it was placed on the market in 1982. We also think that Roche has contributed to these avoidable birth defects by its extensive detailing of the drug.

Roche also failed, although it says that it sent out multiple "Dear Doctor" letters to comply with the applicable FDA regulations concerning mailings to doctors and information on serious drug hazards such as Accutane-induced birth defects by improperly marking the envelopes, etc., on the materials that they sent out at several points in time.

These problems have been largely avoided in the United Kingdom by two measures. The right to prescribe Accutane was restricted to a small group of approximately 200 hospital-based dermatologists from the time that Accutane came on the market in England. It also went on the market with an initial dose of one-half milligram per kilogram per day which is less than the range for which it is recommended in the United States of .5 to one which was decreased from an initial higher range of one to two.

We believe that the historical charge of the

FDA is to insure that all of the drugs that are available to the American public are both safe relative to the condition for which they are being used, and efficacious. Accutane is efficacious but it is not safe if one considers the exposure of thousands of pregnant women or its use for acne which is less severe than that for which it is recommended.

We recognize that the issue of an appropriate remedy for this problem is difficult, and we have given this matter considerable thought. We recommend for a trial period of no more than one year that the FDA modify the approval of the new drug application for Accutane to do several things. One, restrict its availability to board-certified or board-eligible dermatologists who have executed an affidavit swearing that they will abide by the labelling restrictions on the drug. Two, we also believe that it is essential to require that informed consent forms be obtained from all female patients. Three, we feel that the patient package inserts for this drug should be made mandatory, and we also feel that several other restrictions should be placed on the sale of the drug which I will outline subsequently.

Although the absolute number of birth defects that are being caused by this drug has been the subject

of most of the discussion so far this morning, we believe that the question of how many cases of cured severe cystic acne are worth a severely deformed infant, the loss of a wanted pregnancy or the psychologic trauma of an abortion to avoid bearing an affected child is irrelevant. All such tragic outcomes should be avoided if at all possible.

Nevertheless, we just briefly wanted to say that even using a range of assumptions going from Roche's data which is based entirely on reported cases of birth defects up to using data from the National Prescription Audit which documents a considerably higher number of prescriptions being filled than even the estimates used by the FDA that even if all of these estimates, for example, the estimates presented by Dr. Graham this morning, were too high, a problem of major proportions exists. Sixty-two cases of birth defects have been reported, and additional cases continue to occur. We hope that these facts will help us to center the discussion on remedies and not on statistical arguments.

In Roche's rebuttal, Roche accuses the FDA of having made systematic errors in the data analysis. However, in studying Roche's response, Roche appears to have grossly underrepresented the magnitude of the

problem through a number of maneuvers such as calculating the pregnancy exposure rate by using a denominator that includes both male and female patients, patients of all ages, and new and repeat patients.

We conclude, based on data from Roche, based on the FDA data, and on data from the National Prescription Audit, the National Prescription Audit, by the way, which is an industry survey of retail sales of drugs, say that there were 525,000 new prescriptions written for Accutane just in 1986. That is close to four times, over three times the number presented by Roche. We think that estimate is too high because there are multiple prescriptions written for some patients, however. We think that it also points out to Roche's estimate being too low. However, based on using these different sources of data, we also conclude that the annual number of pregnancies exposed to the teratogen lies somewhere between the 39 reported to Roche in 1987, and 6,000 to 7,000 women per year with exposed pregnancies, although it theoretically could be higher.

We come to similar conclusions to those presented by Dr. Graham regarding the number of birth defects which would be seen annually and the number of

abortions. We are also concerned that most central nervous system teratogens are also capable of causing minor neurologic abnormalities. I understand that the Accutane babies are still too young at this point to adequately assess the size of the problem of minor neurologic abnormalities so that some cases which are currently classified as normal births may actually be shown to have other types of problems other than the severe birth defects which have been documented to date.

Also, the data which was adequately presented this morning by Drs. Graham and Kuritsky showing that adverse drug reactions are generally tremendously underreported lead us to conclude that the higher estimates of the number of women exposed and pregnancies exposed annually are likely to be accurate. We do feel that the important point is that any of these levels of exposures resulting in birth defects or abortions is too high.

In its rebuttal to the FDA memorandum, Roche argues that the absolute number of abortions per thousand women of reproductive age rose little in the Michigan data base. We feel this is a cynical manipulation of the data. Roche implies that because women become pregnant at less than the average rate

while on Accutane, the fact that exposed women abort at twice the national rate when they do become pregnant is insignificant. In Michigan, 28 percent of all pregnancies to women on Medicaid ended in legal abortion whereas 60 percent of Accutane exposed pregnancies ended by legal abortion. This is highly significant, as Dr. Graham pointed out this morning.

Roche's argument is only relevant if you think that suffering of families is insignificant. The decision of a family under normal circumstances, of whether to carry a pregnancy to term or to abort an unwanted pregnancy is always difficult. The decision for a family whose infant has been exposed to Accutane whether to abort what might be a wanted pregnancy or perhaps a pregnancy in a family that has religious or philosophical differences with abortion when faced with the prospect of a 25 percent chance of having a deformed infant is a different matter altogether.

We feel that there can be no question but that the doubling of the abortion rate demonstrated in the FDA study amongst Accutane-induced pregnancies guarantees additional psychic and moral trauma for all the families involved. As long a pregnancy exposures continue to occur, legal abortion remains the alternative which most families are likely to choose.

The solution to this problem is not to juggle the columns differently, but to stop pregnancy exposures.

The other question which is being addressed this morning is, is this drug being abused? We totally concur with the analysis presented this morning by Drs. Graham and Kuritsky based on the data from the National Health and Nutrition Examination Survey. We feel that this survey, which was done by a team of over 101 dermatologists using guidelines developed by the American Academy of Dermatology, is the most reliable study to determine the prevalence and incidence of the condition and it is basically the only one that should be used.

We then went on to do a sensitivity analysis which is briefly presented here and basically we come to the conclusion that even if you use a whole variety of assumptions about the severity of acne, about how long it lasts to determine the incidence, about how many of these patients will go on to obtain medical care, it does not matter, you come up with a significant number of women using the drug who do not have the indication for the disease. It may be 1,000, it may be 95 percent wrong, it may be 50 percent, but there is a very significant number. We believe that at least 75 percent of the prescriptions for women are not

for the approved indications for this drug. Even if only one-half of the prescriptions for women were inappropriate, this means that one-half of the birth defects and one-half of the abortions which occur to affected women, occurred to women who did not have a valid reason for using this drug. That is not acceptable. Since pregnancy exposures will occur in direct proportion to the use of the drug, in women of childbearing age, it can be assumed that the majority of pregnancy exposures are therefore occurring in women who did not have the condition for which this drug is approved.

What can be done about this? As Dr. Wolfe said, we petitioned the FDA in 1984 for a number of measures. At that time, we did not urge that it be removed from the market. Since that time, labelling has been strengthened, informative letters sent, non-mandatory patient package inserts and brochures developed. Oh, Sid, can you get out of my bag the little item there? However, neither the total number of prescriptions written for Accutane nor the proportion for women of reproductive age has fallen off significantly. Furthermore, to what extent these measures are being consistently implemented are not clear. Only last week, we tested the voluntary

measures that are supposedly in place in pharmacies. This is admittedly not a statistically significant test, by sending a 35-year-old woman with cystic acne to the drug store around the corner from our office with an Accutane prescription. She never saw a pharmacist at all. She was never asked any questions other than would you like a generic, although there is no generic for Accutane, she received no patient package insert, and she was given this pill bottle which, as you can see, I will give it to the gentleman from Roche first, has no warning sticker relating to pregnancy. She returned the pills to us.

Fairly, Roche has failed in whatever obligation it felt to voluntarily enforce these pharmacy-based measures although, as I say, I do admit this is not a statistically representative sample of United States pharmacies. In any event, even the most rigorous contraception will have a baseline failure rate. Therefore, common sense dictates that the most effective way to reduce the number of exposed pregnancies will be to reduce the number of women using the drug to a bare minimum. Several published studies, including those outlines in the memorandum, the initial FDA memorandum, have examined the difficulties of getting physicians to change their prescribing

practices through traditional education measures. In particular, this have substantiated the lack of efficacy of written materials. The FDA has to regulate drugs in the real world. In this world, doctors are imperfect. Not all dermatologists are academicians. People are not always straightforward about their sexual activity. Women with acne come into offices demanding treatment. Teenagers come to the doctors with their mothers. People give medicines to their friends. Women forget to take their birth control pills. Catholic husbands do not abstain for four months while his wife is taking Accutane, and pregnancy tests are done improperly at times. One of the world's most potent teratogens cannot be left to ride on all these waves of chance.

DR. BERGFELD: Excuse me, how long do you have to go? We are up to 15 minutes.

DR. SILVER: We are up to 15 minutes already?

DR. BERGFELD: Actually we are at 20.

DR. SILVER: We will be another 10 minutes. I would ask for an extension because we are presenting our remedies.

DR. BERGFELD: You have been a little bit redundant. Can you put it together a little bit closer?

DR. SILVER: Basically, the proposals that we want to outline, if that is okay with you, are as follows. We agree with the epidemiologists that Accutane constitutes an imminent hazard to the public health as currently marketed. However, we think that a reasonable alternative to completely removing it from the market exists if and only if the following recommendations are met, we would support maintaining a modified NDA.

The recommendations that we are making are the following. As I mentioned earlier, formally restricting Accutane to board-certified or eligible dermatologists; requiring dermatologists to first file a single, sworn affidavit with the FDA stating that they will adhere to the stated indications for the drug for all patients, and the procedures for the avoidance of pregnancy exposures which will be outlined as below. This affidavit should state that any deviations from the representations will result in, A, withdrawal of prescribing rights for Accutane, and B, possible criminal prosecution for filing false statements.

We believe in mandating written informed consent for all female patients. We feel that the labeling should be changed to reflect any other chronic conditions or other disorders for which Accutane has

been shown to be effective or if not for treatment of those conditions, it should be available through supplemental IND mechanisms. We believe that the risk of severe birth defects, 20 to 25 percent of exposed infants, should be included in the box warning on the labelling. We believe that the box warning on the labelling should also mandate that A, pregnancy tests be performed at least two weeks prior to the onset of therapy, that therapy not commence until the second day after the following menstrual period, that pregnancy tests be performed at monthly intervals thereafter, and that the drug not be prescribed to a woman unless she is using an effective form of contraception which may include abstinence.

There is a series of other recommendations which are included on pages 16 and 17 of the written testimony. We also believe that prescription sizes should be limited for female acne patients to 30 days, and that all patient package inserts and promotional materials should include a photograph of severely affected infants. As you have seen today, the visual impact of the photographs of cystic acne patients is great. This is an effective drug which resolves this condition. We feel that the visual impact of the adverse consequences of pregnancy needs to be equally

graphically represented to people.

We also believe that these precautions should be added to the NDA for etretinate as well given its extraordinary teratogenicity and we will subsequently propose this to the FDA on another occasion. We plan to file a formal petition to the FDA shortly after this hearing on all of these measures that are presented here.

Very briefly, we believe that these measures, although they are quite strong, fall within the legal prerogatives of the FDA to regulate drug usage in the United States, and very briefly, Bill Schultz, who is the attorney from Public Citizen Litigation Group, will present what we understand to be the legal basis for this.

DR. BERGFELD: Mr. Schultz, I will have to ask you to be brief.

MR. SCHULTZ: I will be very brief. There are two or three pages at the end of our testimony that set up a legal argument, and I will not repeat that. I do want to make one point, which is this is obviously a very difficult problem, and I think that everyone on the Committee should search hard to see if there is a way to leave the drug on the market, but to protect the potential victims of the drug, and of course, it is

obvious here the victims are not typical victims because the victims are not really the patients. The victims are unborn children so you have got that additional problem.

We have tried to be creative in finding a way, and essential to our proposal is restricting the use of the drug to dermatologists, the affidavit and the informed consent. I suspect that there is going to be some argument about whether the Agency has the authority to do that, and what I would ask the Committee to do, if it finds this to be a desirable option is to recommend it to the Agency and let the lawyers argue about it later rather than trying to decide this legal issue now. It is my opinion that this is legal. I think there is strong support for that, and obviously, I think the legal issue is best left to another day and another forum. If there are any questions that the Committee has at any time, I would be glad to answer them.

DR. BERGFELD: Well, we are going to take the rest of the speakers that have requested to speak this morning, but we hope that you will be amongst the audience to answer questions when that time comes.

MR. SCHULTZ: I would be happy to.

DR. BERGFELD: Thank you. Thank you for your

presentations. I have before me a list of seven speakers that we have, that we are knowledgeable about, and I am sure there are others that are in the invited guest area that may wish to speak. I am going to request that only those who have prepared presentations present, and that also that the presentation be five minutes or less. I am sorry if you have to redo your presentation at this time, but unless we do this, we will not hear those who have something to say.

I have in front of me the fact that Dr. Grabowski, the President of the Teratology Society would like to make a brief presentation.

DR. GRABOWSKI: I will be brief.

DR. BERGFELD: Thank you.

DR. GRABOWSKI: I am Casiminer Grabowski, I am Professor and Chairman of the Department of Biology at the University of Miami, and President of the Teratology Society. The Teratology Society is a professional organization of basic scientists, pediatricians, obstetricians, toxicologists and other health scientists concerns with both the itiology and prevention of birth defects as well as other aspects of abnormal development. Members of the Teratology Society are from academia, government, private industry and the statements that I am giving here have been

reviewed and approved by the Council of the Society as well as the Public Affairs Committee of the Teratology Society.

As a professional scientific society, we echo the concerns expressed here today, concerns about the teratogenicity and other developmental effects of retinoids. Many, if not most of the studies demonstrating such effects of retinoids have been conducted by members of the Teratology Society. Our Public Affairs Committee prepared and released in April of 1987 a statement expressing concern about the potential teratogenicity of large doses of Vitamin A available in the forms of retinol/retinyl esters. That statement also reviewed the present state of knowledge concerning the developmental toxicity of isotretinoin and etretinate in humans as well as in animals. These two synthetic retinoids are currently approved by the Food and Drug Administration for oral use in the effective therapy for recalcitrant cystic acne and psoraisis respectively. A copy of the document from the Society has been provided to all members of the Committee.

The current labelling of isotretinoin reflects concern for defects in humans, birth defects in humans. The recommendations to perform a pregnancy

test and to begin contraception prior to the initiation of therapy is certainly well justified. The warnings also state that women who become pregnant while using isotretinoin should discuss with their physician the desirability of continuing the pregnancy.

Among the drugs on the market, the current label for isotretinoin is one of the most specific and detailed warnings concerning teratogenic risk. In spite of this detailed labelling, in package inserts, on bottles, advertisements, women do continue to become pregnant while using isotretinoin, and some of these women elect to continue their pregnancies to term. Among pregnancies that continue to term, the risk of birth defects is reported to be about 25 percent. An additional new information presented by Dr. Edward Lammer of the California Birth Defects Monitoring Program, relates to the severity of the birth defects following prenatal exposure to isotretinoin. Of the malformed children who have been identified, 40 to 50 percent have died before the age of four years. Those babies born to mothers consuming isotretinoin at therapeutic levels during their pregnancies do have life-threatening birth defects.

Now, well-crafted strategies may allow safe use of a teratogenic drugs. Like isotretinoin,

thalidomide poses a risk of malformations. The risk of malformations resulting from thalidomide exposure during the first trimester has been estimated to be about 20 percent, possibly higher during these specific early days of gestation. Since the mid-1960's, thalidomide has been used effectively in the treatment of Erythema nodosum leprosum. This therapy with thalidomide in a limited population has been made available in the United States under an investigational new drug process, and women of reproductive age who require thalidomide therapy can be treated under very strict, hospital supervision. It is important to determine whether the current approach for thalidomide is at all relevant for isotretinoin or whether there are other options to be considered by this Committee.

We all face a difficult situation regarding the appropriate use of this widely-used, effective therapeutic agent. Despite specific and detailed labelling against the use of isotretinoin during pregnancy, malformed babies do continue to be born because of inappropriate use. New and more effective means are required to prevent exposures to isotretinoin during pregnancy. In the study of 154 isotretinoin exposed pregnancies, Lammer and associates obtained data on contraceptive use for 99 of these pregnancies.

Approximately one-third of the women were pregnant were pregnancy before the isotretinoin was prescribed. One-third became pregnant because contraception was not used, and one-third became pregnant because of reported contraceptive failure. These data indicate that even with attempts at contraception, exposures to isotretinoin during pregnancy have occurred and will continue to occur unless additional effective strategies are found to prevent pregnancy exposures.

Now, we as a Society are not offering any specific regulatory recommendation. We stand by to assist your efforts in providing expertise in developmental toxicity. In summary, it must be noted that the isotretinoin embryopathy is fully preventable. More must be done to prevent exposure to isotretinoin during pregnancy. Therefore, the Teratology Society most strongly urges this Committee, the Food and Drug Administration, and the manufacturers of synthetic retinoids to seek additional strategies to make isotretinoin available to those who can benefit from it without causing harm to developing humans. Thank you.

DR. BERGFELD: Thank you. Our next speaker is Dr. James Hanson, on behalf of the March of Dimes Birth Defects Foundation. Dr. Hanson.

DR. HANSON: My name is James Hanson. I am Director of the Division of Medical Genetics and Professor of Pediatrics at the University of Iowa College of Medicine. I might also add that I operate a teratogen information service for the state and the region and direct a statewide birth defects registry surveillance program. I am testifying here today on behalf of the March of Dimes Birth Defects Foundation. We believe that the scientific data clearly show that Accutane, isotretinoin, is a human teratogen, causing, among other defects, severe and life threatening lesions to the central nervous system, heart and cranial facial structures.

The magnitude of the risk for such severe outcomes is sufficiently high to make use during pregnancy absolutely contraindicated from the standpoint of fetal welfare. The risks to the exposed fetus far outweigh the advantages accruing to patients treated with this agent. Accutane is likely to be used by women of childbearing age, particularly adolescents who may be unaware both of their pregnancy and the risks posed by the drug. Despite current stringent warnings regarding the use of Accutane in women pregnant or likely to be, pregnancies are still occurring with severe consequences to the fetus. If

the FDA concludes that there is a compelling reason for permitting this drug to continue to be prescribed for certain women patients for whom there is no other safe and effective therapy, the March of Dimes Birth Defects Foundation strongly urges that the drug be available only through a highly-controlled system, thus precluding general or indiscriminate use.

There should be a limited number of centers and specialists permitted to prescribe the drug, a meticulous program of screening, support, and follow up services for treated patients must be mandatory, and the method of insuring informed consent should be provided. It should be added that the March of Dimes Birth Defects Foundation concern for fetal welfare extends beyond isotretinoin to other similar chemically related drugs such as etretinate, retinol and retinyl esters of Vitamin A.

I wish to personally re-emphasize two of these points. Number one is that exposures and damage to babies are still occurring. I personally have received such calls within the past two months. Secondly, I would ask whether or not it really matters whether there are 60, 600, 1,600 damaged or dead babies. The lower figures are certainly under-estimates but the question is how many is enough to counter balance the

needs of severely effected adults, the numbers of which are equally open to question. It seems to me that it is very important to emphasize the last point from the March of Dimes, and that is that if this drug is to continue to be prescribed, there must be a system developed which will minimized risk to the fetus, and that will require a more structured and regulated system which not only assures informed consent, but a system of support, counselling, and follow-up services which really must include some kind of ongoing evaluation of any programmatic changes effectiveness.

The small numbers of new appropriately treated patients per M.D., by either the estimates of the FDA or the company, seems to me to be a strong argument for both the feasibility of and the need for a restricted group of provider programs. Thank you for your attention.

DR. BERGFELD: Thank you for your comments, Dr. Hanson. The next presenter is Dr. Robert L. Brent, on behalf of the American Academy of Pediatrics, Genetic Committee. Dr. Brent?

DR. BRENT: It is still morning so I will say good morning to the Committee members. Thank you for giving the Academy the opportunity present this statement before your Committee. I am Robert L. Brent,

Professor and Chairman of the Department of Pediatrics at Jefferson Medical College. My field of interest is clinical and experimental teratology and I have been doing research on the causes of birth defects for the past 30 years. I am probably in a somewhat unique, and also, having started a pediatric dermatology clinic in our department, and therefore have seen the dermatology clinic patients for the last 20 years.

I would like to read and probably eliminate some of the redundant material from the Academy statement first and then make a number of comments. I have been asked by the American Academy of Pediatrics to present their concerns and recommendations dealing with the oral administration of isotretinoin. This statement has been approved by the Executive Committee of the American Academy of Pediatrics which represents over 34,000 pediatricians whose concern is the welfare of children in this country.

Birth defects are an important contributor to the morbidity and mortality of children in our country, and therefore the prevention of birth defects is a high priority of the American Academy of Pediatrics. We are concerned about the numerous reports, and I am going to skip two paragraphs and just state, my concern after listening to the presentation this morning is that we

are worried about orders of magnitude or where the decimal point is, and the fact is I doubt whether there is an individual in this room that is not support the notion that this is a potent teratogen and that it is producing birth defects. How you can get away from that conclusion by manipulating or changing data is beyond I think, anybody's ability to change data.

Secondly, therefore, in talking about the number of birth defects, I think at this point it is irrelevant. It is a significant health problem, and the fact is children are being born every year because of the exposure to this drug. This is a relatively easy determination to make because of the fact that the syndrome is quite specific and, as with many birth defect syndromes the nature of the defects, as I imagine Dr. Lammer will tell you later today, helps you to be more certain about the itiology of an exposure in a particular case or in a group of cases.

I will not mention the precautions because the precautions that are listed in the PDR and the package insert, are as has been mentioned by both the FDA and the Hoffman-La Roche Company, the strongest that have even been introduced, and yet it is not working. I think that is the bottom line, the fact is that there are still pregnancies, and if you want to argue about

where the number is, there are exposures that are occurring in pregnant women who are on this drug. Dr. Lammer will probably be talking about the proportions but the thing that is amazing is that women at this time, in this country, are still being put on the drug who are pregnant. Forget about the pregnancy failures, the fact is women who are pregnant have been put on the drug.

The AAP recognizes that your Committee has a difficult task, probably one of the most difficult that any Committee has ever faced. While there may be several acceptable plans for modifying the usage of isotretinoin, it should be pointed out that etretinate, something that we discussed very little here today, presents such a serious, long standing risk after administration, for such long periods of time, that there is no alternative but to remove it from use in women with reproductive potential.

With regard to isotretinoin, the simplest suggestion for preventing its potential for producing birth defects is to prevent its use in women with reproductive potential by removing it from the market. What other alternatives are there? The FDA could limit the use of the drug to a select group of physicians which others have alluded to, who would prescribe the

drug in a more controlled fashion, and be directly responsible for dispensing the drug rather than prescribing it. Further research is needed to determine possibly whether lower levels of the drug might be effective, and they might not be teratogenic, and this actually could be done effectively in some of the primate models because of the great similarity between primate teratology with isotretinoin and human teratology.

Your Committee has a serious problem to consider. One this is certain, you cannot maintain the present guidelines for using isotretinoin. Either the drug has to be removed from the market, or a foolproof plan of guaranteeing that pregnancy exposure does not occur must be adopted.

I just have a few brief comments with regard to some of the statements that have been made, and additions to my own presentation. What I mean by a designated physician is the physician who prescribes a drug, but dispenses it. There is a much, the element of control, once you write a prescription, and it leaves your office, is the fact that the drug can be used by other people, and I think that in the control area, whether it is the dermatologist or the dermatologist in conjunction with an

obstetrician-reproductive biologist so the two could work together, I think an important element is dispensing the drug from that clinic in allocated amounts which would cover a short period of time.

Secondly, I would like to comment about a number of suggestions that have been made with regard to pregnancy tests. I gather that Dr. Wolfe's group, suggesting monthly pregnancy tests, reflects probably that group's unsophistication in the area of embryology. In actuality, a weekly pregnancy test would not suffice. This teratogen is one of the earliest effective teratogens. It probably effects the embryo at the time of gastrulation. The way that you can make that determination is a malformed embryo that has severe ear defects lets you know that this is a very early onset in sensitivity. If that is true, and the pregnancy test sensitivity is, say, at 10 days, that would mean that a woman could come in on the ninth day, have her pregnancy test negative, come in the next week, be then at nine plus seven, plus 16 days, you stop the medication, it is still going to be in her system until the moment of gastrulation. You might end up with worse birth defects you would eliminate the abortion statistic.

I am just giving you that as a hypothesis.

The fact is I want to point out to the Committee this is a very difficult problem to circumvent. My goal would be the prevention of pregnancy, and I am telling you that with the most sophisticated techniques we have not, it is a very difficult problem.

Secondly, oral contraceptive have been suggested. Combine them. Well, that would be the most ridiculous thing because all the women has to do is skip two pills of a combined oral contraceptive and Accutane and now you have a woman who thinks she cannot get pregnant who is going to get pregnant so that cannot be done.

One other suggestion that has been made is an injection of a drug which is not approved in the United States, namely Depo Provera which gives you six months of infertility, and a two-month prescription which in a sense would be probably the best answer, but we cannot introduce that at this time because the drug is not available in the United States. Finally, my experience must be very unusual because I admit we have a very small pediatric dermatology clinic. We only see five to ten patients a week, and over the last number of years, since Accutane was introduced, I have only used the drug four times.

In closing, I do not envy your task. You have

Teratology Society, Dr. Grabowski's group, and in the pediatric group, those of us who have knowledge in reproductive biology, would be more than happy to help you with some of the physiological aspects of pregnancy in the sensitivity period of the human embryo to this agent because I think they will be important aspects in the determination of how this drug will be dispensed and used. Thank you very much for your attention.

DR. BERGFELD: Thank you, Doctor. We have scheduled four other presenters, and hopefully we will be breaking at 12:30 for lunch. Dr. Nancy Lee, Division of Reproduction Health, Centers of Disease Control, Atlanta, Georgia.

DR. LEE: Good day. I am not going to be here to talk about Accutane or cystic acne. I have been asked to present something on contraceptive failure. I guess it is background information for the use of the Committee. I am a medical epidemiologist with the Division of Reproductive Health, and I would like to acknowledge that most of the information that I am going to be presenting today is not work done by the CDC, but work done by some population demographers at Princeton, headed up by Dr. James Trussell and Katherine Coast who have put together basically what

has quickly become the definitive review of contraceptive efficacy in this country. So I would just like to acknowledge the work of Dr. Trussell. This work, these rates were quickly adopted by Planned Parenthood and the American College of OB-GYN for their patient and physician education literature.

I am going to talk about contraceptive failure rates. There are basically two failure rates which we need to keep in mind. One is the lowest expected. That is, the expected pregnancy rate among perfect users of the method. This is basically what other people this morning have referred to as method failure. I point out this is expected, and most experts believe that you basically have to sort of make a ballpark guess. The next rate, which is perhaps what I believe is the rate that the Committee is probably most interested in is the typical pregnancy rate, and that is the rate observed among actual users, and this includes pregnancies due to imperfect use of the method, and to failure of the method itself. Most, in the work I am going to be presenting this morning, most of those typical pregnancy rates are rates that have come from the National Survey of Family Growth, another nationwide random survey done by NCHS of women of reproductive age.

These rates are usually presented as the number of pregnancies per 100 users of that method. The lowest expected rate is useful when counselling highly motivated users but I think a more reasonable, for women whose motivation you are not quite sure of, the typical pregnancy rate may be more useful. These are first year contraceptive failure rates, and these are the rates that are usually used. I might add that over time, in the second and third years, the rates tend to improve, and it is kind of obvious probably why that occurs. Women know how to use contraceptives better, and more importantly, the failures occur, but these are the ones that are probably the most important to consider.

The lowest expected are rates in the first column of numbers, the typical are in the second column, and as I said, I believe that for the purposes we are discussing this morning, the typical rates are the ones that are probably the most important to consider. Note that the pill has a very low rate for the lowest expected, but even with the typical rate, it is three percent per year, that is, three pregnancies in the first year of contraceptive use. The IUD which is probably going to be more widely available shortly, has also a low expected, the typical is a little bit

higher than the pill. Most of these method and user failures are probably related to expulsion which occurs with IUD's which goes undetected. Someone earlier mentioned Depo Provera. These have very low expected and typical failure rates, although I might add that I imagine that the typical failure rate is a little bit higher than .4 percent if only because a woman must return to her provider every three months for an injection so it does require that minimal compliance.

Then we get into the barrier methods. As you will notice, all of the barrier methods basically have nice, low, lowest expected rates, between two and really five percent probably. However, they have much wider discrepancy in their typical failure rates, and this is because they are so, they so rely on consistent and highly motivated use. Their typical failure rates are quite a bit higher than the rates of the three previous methods that I provided for you.

The last two methods that I have listed are sterilization methods. Those obviously have very low, lowest expected and typical failure rates, and so are very useful in those women who have completed their childbearing, though of course, note that we still have two to four per thousand pregnancies per year with these rates. And I might just put at the bottom that

in several populations of fecund women who are not using any method, they come up over and over again with approximately 89 percent of women who use no method of contraception for a year will become pregnant, 89 percent.

Now, I want to give you a brief overview of the considerations that contraceptive providers and women need to make when choosing a contraceptive method. Generally, we consider efficacy, safety, compliance requirements, personal medical considerations and reversability I want to underscore, no contraceptive is perfect. I wish it were, there was one, but none is perfect. All the methods I have listed on the slide are generally safe. Each may have certain side effects which, while not dangerous, affect a woman's choice of contraceptives. Each may also have certain theoretical or real adverse effects which must be weighed when choosing a method of birth control.

What I have put up here is a subjective measure of efficacy and something about the compliance that is required, and then something about who providers not necessarily when considering about Accutane use, but in general how they make decisions. The pill is a very effective method. Daily compliance

is necessary, and it is a good choice for young women who want to delay childbearing because fertility is not damaged, it is a very effective method. The IUD is also a very effective method. Minimum compliance is required, basically checking to make sure expulsion has not occurred. There is definitely a risk of pelvic inflammatory disease and infertility and hence, what we recommend is that it is a good choice for women at low risk for sexually transmitted diseases and for those who have completed their childbearing, and probably is not a good method of first choice for women who want to have children in the future.

Barrier methods are moderately effective methods as opposed to very effective. They require highly motivated users, and they are a good choice for women at high risk for STD's. Injectables, for example, Depo Provera, these are injectable progestins which are very effective, minimum compliance is required, for example, they just need to return to their physician every three months for an injection, there is no permanent effect on fertility although resumption of ovulation may be delayed for four to nine months. None is licensed for contraceptive use in the United States, although Depo Provera is available in this country for use for other purposes.

Sterilization is a very effective method. No compliance is required, and it is obviously indicated for those who do not want more children. Basically we should not think about sterilization reversal. From the National Survey of Family Growth, they came up, which is the survey which we used to get the typical failure rates, we came up with risk factors for contraceptive failure. The risk is higher for younger women. It is higher for low income women, it is higher for women of higher parity, and the third one may be, because of the fourth one, it is higher for women seeking to delay a wanted pregnancy than to prevent an unwanted pregnancy. Risk is also higher for married women, although much of the difference is probably explained by underreporting of induced abortion among non-married women.

Now I would like to end my presentation with a brief discussion of contraceptive use in teens because Accutane may be used more heavily in the younger age group. Insufficient data exists to obtain contraceptive failure rates for teens similar to those that I have presented already. However, I would like to focus on the problems of contraceptive use in teens from what we know from several surveys of teens. I am presenting this information on this slide about the use

of any contraceptive at first intercourse by teens. Overall, about one-half of teens use any type of contraception at first intercourse. That is the middle column of numbers there. Only about 20 percent use a prescription method, IUD's, pills or diaphragms, which are likely to be more effective. I imagine that, though they lump those, I imagine that most of that use is going to end up being the birth control pill.

So as you can see here, when they come to their episode of first intercourse, half of teenage women are unprotected, and the kinds, a lot of them do not use a very safe or very effective form of contraception at that. Another important point to remember is that on average, the delay between first intercourse and use of a prescription method is one year. Another interesting fact is that one-half of all teen pregnancies occur within the first six months of initiating intercourse.

Once all of this, they have initiated sexual activity and have begun to get into the system, among sexually active teenagers, 68 percent recorded contraceptive use at last intercourse. This is not the first intercourse, this is the last intercourse that they had; 62 percent used the pill, 29 percent used barrier methods of some sort, and 9 percent used other

methods.

Why do so many teens fail to use contraception even though they do not want to become pregnant? More than half thought they could not conceive. Others had not expected to have intercourse, and especially among examining the reason among women who did not use a contraceptive with their first intercourse, most of them said they had not expected to have intercourse that first time that they had it.

I would just like to finish my presentation with a results from modeling done using data from the vital statistics data and the National Survey of Family Growth which estimates the percent of women in this country who will have their first pregnancy before age 20. As you can see, almost half will have had their first pregnancy by age 20. There is some difference by racial group. Thank you very much.

DR. BERGFELD: Thank you. We need to move on because we have less than 10 minutes to have our next few speakers present. The next is Dr. Lammer, and he is from the California Birth Defects Monitoring Program. Dr. Lammer.

DR. LAMMER: Dr. Bergfeld, I thought this morning was intended for people to present data, but I do not really feel I can do justice to the information

I have with only five minutes of time.

DR. BERGFELD: We can postpone you then to the afternoon session.

DR. LAMMER: I would prefer that.

DR. BERGFELD: Thank you. Dr. Gary Peck has requested to present. Dr. Peck, who is from the NIH, Senipr Investigator, Dermatology Branch.

DR. G. PECK: I would like to thank Dr. Evans for inviting me to participate at this meeting as a guest of the FDA. My remarks are intended to broaden the context of this discussion, and then end up back on target on teratogenicity. My first concern is that if Accutane is indeed withdrawn from the market, that the next this is that Tegison will go, and then, in this environment, the entire class of retinoids may go because they are, in effect, we must assume that all of them are teratogens. Having spent my career, I say that from someone who has the perspective of having spent his research career in studying retinoids.

Concerning the topic of medical need, first, for acne, it is quite clear in this extreme case that Accutane would be indicated. It is a woman in her 30's who has had 20 years of conventional therapy. I think the greater question is what Dr. Shalita raised is what about the other end of the spectrum, how many scars do

you need, how many new acne cysts do you need while on conventional therapy? How long do you have to remain on conventional therapy before you are deemed adequate to have Accutane. I think this decision may vary with each physician and perhaps the Committee should discuss the other end of the spectrum in their discussions.

In addition to cystic acne, we have other acne-formed diseases such as acne fulmanant occurring in a 12-year-old boy, and in terms of psychic suffering, you could imagine what would happen if Accutane were not on the market, what his adolescence would have been like. Also, in Meyhans hidradenitis suppurativa where no other therapy was effective, here at pretreatment, this man received two milligrams per kilo, and had an excellent response.

I turn you now, I now wear the hat as a member of the Board of FIRST which is the Foundation for Ichthyoses and Related Skin Types, and I want to remind you that in the initial NDA, disorders of keratonization, including the ichthyoses were included, and for many of the patients, even if you are among those who would say, well, acne, regardless of how severe, is trivial, I do not think you can say about disorders of keratonization. I would say that these patients rely on the retinoids for their ability to

function in society, for their survival in the sense that they, when I had a psychiatrist interview 22 of them,there is Darier's Disease, there is inflammatory Darier's Disease, epidermal retikyper(?) keratosis, Lamelor ichthyosis, and Harlequin fetus who would have died without retinoids, and did survive, but my point being that these patients were interviewed by psychiatrists and 10 out of 22 had either suicidal attempts, suicidal plans, or had recurrent suicidal thoughts. Although it is not an indication at the moment, I would hope that in the future it might be.

Also, I am now wearing the hat as a cancer researcher who has been using retinoids for initially therapy but not chemoprevention of cancer, skin cancer from a variety of ideologies. I think that this is something that we should consider in this discussion as being down the road or in the future, a future indication. For example, here is a patient with xeroderma pigmentosum whose affected brother died of this disease skin cancers, and we have a study in which we have treated five of these patients with isotretinoin for two years at two milligrams per kilo, and is, if you look at the incidence of lesions during treatment and compare it with the before treatment and post-treatment figures, you can see that there is a

drug. Interestingly, this past year, there was an article by Lippman and Meyskens where squamous cell carcinoma which had either been recurrent or metastatic had responded to oral isotretinoin in one milligram per kilo with either complete or partial regression. In addition to skin cancer, Meyskens has used this to achieve complete regression in choriocarcinoma and partial regressions in mycosis fungoidis. Finally, there are now four case reports of complete responses with isotretinoin known in acute promyelocytic leukemia which induced a terminal differentiation of these leukemic promyelocytes.

I would like to finish up with teratogenicity, and what I am doing in my own clinical practice. In patients who have acne that is limited to the face, and they have fewer than 15 cysts, is that I am trying a short term high dose dosage schedule at two milligram per kilo for two weeks so in a woman, and it could be up to four weeks, but in a woman it could be limited to, in effect, one menstrual cycle. The advantages of this would be obvious, that you would have a decreased duration of acute toxicities, decreased risk of the rate of graphic abnormality dish which in our hands is dose dependent, decreased risk of teratogenicity in

to five months, and decreased expense of the drug.

This was based on results that I did from a study in 1981, the three-arm randomized double blind study involving 72 patients, and of those 72, I had five who had fewer than 15 acne cysts of the face or actual mean of about 12. They were treated at two milligrams per kilo for two weeks, and then 14 weeks of placebo. At the end of the two weeks of isotretinoin, they had a 33 percent improvement. At the end of the placebo, these five patients had an 85 percent, and four weeks later, just after observation, with no therapy, this improvement continued. So when I use this in my clinic now, I find that some patients may have a complete response, some patient may have partial response but where they have been unresponsive to conventional therapy, I find that when I reintroduce conventional therapy, they do respond. In those patients who do not respond to this short term, high dose schedule, I then will treat with a standard currently recommended schedule of one milligram per kilo for five months but in effect what I am doing is I am reducing the total number of patients who do require the standard therapy. Thank you for your attention.

DR. BERGFELD: To my knowledge, the last

Thomas Rogers, an attorney. Mr. Rogers? Mr. Rogers, will you state who you represent when you reach the microphone, please?

MR. ROGERS: My name is Tom Rogers. I am an attorney with the law firm of Ness, Motley in Charleston, South Carolina. I represent two plaintiffs in pending litigation involving Accutane. I am also appearing on behalf of the Association of Trial Lawyers of America, their Accutane Litigation Subgroup. I think that with the exception of the statements made by the individuals from the Health Research Group, there has been inadequate attention paid today to the role of the manufacturer in creating this situation. I think that Dr. Wolfe's comments concerning the outrageousness of their conduct in failing to require a pregnancy test prior to administration of the drug when it was first released in September 1982, which extended through the large part of 1983, is crucial to bear in mind in viewing this situation. Both of my clients were prescribed the drug in 1983. Both of them did not receive pregnancy tests. Both of them gave birth to children afflicted with the Accutane syndrome.

I think I want to keep my comments brief, but I would like to point out that regardless of the

described as radical approaches taken to insuring that the information concerning the birth defects associated with the drug were conveyed to the doctors and conveyed to the patients, ultimately, those approaches were diminished, the effectiveness of those approaches were diminished by the overpromotion that Hoffman-La Roche has engaged in with respect to this drug. The drug is not being prescribed just by dermatologists. Dermatologists admittedly, as we have heard today in statements by various individuals, dermatologists would be more familiar with the risks associated with retinoids of the class and with Accutane as a particular drug. Unfortunately, in both of my cases, the drug was prescribed by non-dermatologists.

I think, looking at the amount of prescriptions we have over the past six years, it is clear that the controls, the restrictions suggested even in the original warnings were not being observed, the drug was being prescribed outside of the chronic recalcitrant cystic acne area, and that essentially there, in addition to the powers that the FDA has to correct this situation, there are other factors at work in our system including the judicial system, that will play a role as time goes on. Thank you.

remarks. We have now 12:30 and I would like to ask at this time before we adjourn for lunch, if there are any other guests that I do not have listed, we are going to put Dr. Lammer at the beginning of the next session. Are there any other guests that wish to speak at that time, or have prepared presentations? Would you see me so I can get your name? If there are not, then we will adjourn for lunch. We will resume at 1:30 sharp, and we will continue the consideration of Accutane.

(LUNCH BREAK)

DR. BERGFELD: If I might have your attention please, we would like to begin the afternoon session if you all would sit down. As the Committee is being seated and some of the guests are being seated, I would like to announce that we have somewhat of a shortened period of time since we have not completed some of the presentations from this morning which deal with the data. We will need to finish up our morning presentations by at least ten after two. We will be having two presentations from guests, and at the end of that time, the Committee will need to have some discussion time. We will then move on to the options that are presented to the Committee, the quest for restricting the drug Accutane, and during that time the

representatives from Hoffman-La Roche, the CDC. To my knowledge, we have no guests that have asked to speak during that time, and then the Committee discussion as to what direction they will be taking.

It gives me great pleasure at this time to introduce Commissioner Young who has just joined us for the afternoon session. Commissioner?

DR. YOUNG: Thank you. I do not need to say anything. It has been all said. Thank you.

DR. BERGFELD: An announcement to be made, a press room has been set up in the Maryland Room for this afternoon's session. I would like to request that if there are any interviews to be done they be not done in this room, but everyone adjourn to the Maryland Room. Thank you. If Dr. Lammer can now present? Again, Dr. Lammer is from the California Birth Defects Monitoring Program, Berkeley Regional Office, Berkeley, California, and I understand your name is pronounced Lammer. Pardon me.

DR. LAMMER: My name is Ed Lammer, and thank you for giving me a few extra minutes, Dr. Bergfeld. For the past four years, I have been the principal investigator of the only comprehensive studies to my knowledge of Accutane exposure and adverse reproductive

morning that the hearing would be dominated by debate over the validity of the findings from the FDA memorandum when there was already a substantial amount of information about Accutane and birth defects to justify having this hearing held. I would just like to reiterate what several other people have already said which is that I do not think that the numbers game is really the issue here, and I do not think it is relevant whether there are 62 or 1,000 babies who are malformed by this drug. The generic issues are still there, and I do not think we should spend a lot of time arguing over how those numbers in the memorandum were derived.

I think a more important issue for debate is what appears to be the absence of any major criteria for deciding whether regulatory intervention is warranted for medications that are first efficacious, then second have limited maternal toxicity, but are highly teratogenic. When I summarize, I hope to have one suggestion to make in that regard. Can I have the slides on please?

Now, this is just a histogram showing the number of malformed fetuses that I am aware of who have been identified in North America since 1983, and again

have seen before, primarily because I limited this slide to fetuses that were potentially viable, that is, who reached the gestational age of at least 20 weeks. Since this slide was created last month, there has been one more child born in 1988, one in 1987, and one child I have identified just in the last month born in 1984 so it is clearly a problem that is not going away, although the numbers, at least that we have identified to date are not as great as they were in the first few years that the drug was marketed.

This is a geographical distribution showing all of the cases of children who had at least one major birth defect who were known to me as of one year ago. The yellow dots indicate children who were alive at that time. The blue dots indicate all the children who died as a result of these birth defects, and none of these deaths include fetuses that were electively terminated because of prenatally diagnosed abnormalities. We are basically following two populations of children. The first is a group of prospectively identified pregnancies. That is, a group of women who were identified to us during the pregnancy itself before we had any knowledge of the fetal outcome, that is, before there was any fetal

etc. That group we followed because it gives us an unbiased spectrum of the whole range of potential outcomes that can result from this exposure. The other group of children that we study are a group of children who are identified retrospectively. That is, they were born with birth defects and were reported and the exposure information was obtained because they were born with these birth defects. The source of these pregnancies and the children are reports made to the manufacturer, Hoffman-La Roche, to the Food and Drug Administration, where Dr. Rosa has helped me extensively or phone calls that have come in directly to me over the last few years because of our known interest in this subject.

Now, basically the purpose of the studies we have been conducting is to quantify the absolute risks for spontaneous abortion, major birth defects, minor abnormalities, hormonal deficiencies which some of these children have, sensory deficits, hearing and vision primarily. We are tracking their longitudinal growth, and we are doing studies to look at the, compare the exposure intervals and dose with the various outcomes. Then, we are also trying to get information to determine the factors that contribute to

to present because of the time limitations are our information on absolute risks for spontaneous abortion and major malformation and some of the information I have about risks for major malformation related to maternal daily dose.

The first slide, again, all the information I am going to present only concerns the group of pregnancies that we have identified and followed prospectively, and that is the group that you can use to determine and quantify these absolute risks. Now, we followed 30 pregnancies that were identified before the completion of the 13th week after the LMP so these are pregnancies that would be identified before the end of the period when most spontaneous abortions would occur, and contrary to the findings that we heard earlier today, we found that in pregnancies that we identify relatively early, the risk for spontaneous abortion is 40 percent, 12 out of 30 pregnancies. There is one pregnancy with a spontaneous abortion identified prospectively for which we did not have good enough gestational age information to know whether it was identified before the 13th week so again, if you identify pregnancies early enough, the risk for spontaneous abortion is much higher than the figures

For the children who reached 20 weeks and beyond, we conduct these following evaluations. We do a standardized physical examinations with definitions for minor abnormalities, we examine each one of these children, two pediatricians do the exam. One performs a blind assessment without knowledge of the fetus's exposure status. The other pediatrician, myself, does an unblinded exam. We photograph the children. We have done CBC's, calcium phosphate, parathyroid hormone, calcitonin. We have arranged for all of these children to have otolaryngology assessments and ophthalmology exams. We arrange for them to have hearing evaluations which generally consist of auditory evoked response testing. We interview the mothers with a standard interview to get at potential confounding factors, and other potential causes for birth defects and other adverse reproductive outcomes, and we obtain copies of the maternal and infant medical records, x-ray studies, etc., and we attempt to document the dose and timing of the maternal exposure by obtaining pharmacy records, and when that is not possible, we try to obtain records of the prescribing physician. So the evaluations are quite extensive, and I think we do as good a job as we can do of documenting that in fact

Now, over the past two years, these are all the locations we have travelled to examine these children, from northern Quebec to Puerto Rico to Honolulu. The yellow dots indicate the children who we examined from the prospectively ascertained cohort. The blue dots represent children with birth defects who were reported retrospectively, and we have followed these three red dots. Now we have four children who we have identified whose exposures were isolated to the second trimester of the pregnancy.

Basically, to summarize those outcomes, if the pregnancy reaches 20 weeks or beyond, we found that 11 out of 52 children had at least one major structural birth defect, and that is where the figure of 25 percent that you heard this morning came from so again we have followed 65 pregnancies prospectively, 13 ended in spontaneous abortion, and of the pregnancies that reach 20 weeks or beyond, 25 percent of those infants had major birth defects.

When we look at the mortality experience, in our prospectively ascertained group, there have been three deaths, one due to sudden infant death syndrome without birth defects, two children died from birth defects probably caused by the medication whereas in

that 60 percent of these children die so basically the way that I would use this information is that in the prospective group, two of the eleven children with major birth defects have died which is approximately 20 percent mortality whereas in the retrospectively reported children, 60 percent of the children with birth defects die. This suggests that the group who are identified retrospectively have much more severe disease, and in fact when we looked at the types of birth defects that the children identified prospectively, versus the ones who were identified retrospectively, the types of birth defects they have are slightly different in that this group tends to have children with much higher frequency of congenital heart defects, many of which cannot be repaired and is frequently the cause of death in those children.

We have used that information to make this summary, that first the risk for spontaneous abortion again is for pregnancies that are identified early is 40 percent. The absolute risk that a child would have at least one major malformation following isotretinoin when used in the first trimester, is almost 25 percent, and that the pattern of malformation among infants and fetuses in the prospective cohort differs from that

cases in that cardiac malformations were much less frequent in the prospective cohort.

The mortality experience was also three times higher in the retrospectively ascertained cases, and I think that this is, the information suggests that there is probably significant underreporting, particularly of less severely affected exposed infants and especially those who have only central nervous system, and/or cranial/facial malformations.

This shows some of the spectrum of defects. This is a child who had congenital hydrocephalus, teratology below, had no ears on the left side, no ear on the right side, and absent parathyroid gland, absent thymus gland. I should stop and mention that this drug causes very specific birth defects. It does not increase the overall risk for birth defects. It has specific effects on the developing central nervous system, cranial/facial development, cardiac and great vessel development, the thymus gland, and the parathyroid gland. We rarely see any problems outside of those areas,, and there is accumulating evidence now to suggest that those organs are particularly susceptible, probably because all trans-retinoic acid plays an extensive role in controlling normal embryonic

basically mucks up that whole process by providing too much of a chemical that is playing a major control over normal development.

Another child with congenital hydrocephalus, low set malformed ear, heart defect, absent thymus gland. Another child who is surviving has this characteristic ear malformation which is very typical of malformations induced by thalidomide, and has as well an ipsilateral facial nerve paralysis. Another child who has hypertelorism, a wide space between the eyes, blindness, deafness, asymmetric pupils, microcephaly, and essentially has made no developmental progress since birth. Another child with a severe ear malformation.

Now, this, I just want to show a couple of slides to demonstrate the value of this kind of longitudinal follow up. Here is a baby described as normal at birth who is quite cute I would say, and has a very normal looking facial appearance. I want to show a series of slides showing maldevelopment of the mid-portion of her face which is not present at birth, but appears later as she gets older. Here is another photo of her at six months, at one year you see she has got this mid-facial underdevelopment with epicanthal

examined her for the study at about three years of age. She has the epicanthal folds, this characteristic nose shape, short nose, underdevelopment of this midline portion of her face which would not have been detectable had she only been evaluated at birth. This gives you some idea of the mild end of the spectrum of effects. Now, I just want to show one more slide in case people have any ideas that one of the possible regulatory interventions might be to recommend that this drug might be safer if used at lower doses as has been suggested in a letter to Lancet by Dr. Rosa.

We looked at dose outcome relationships, and we looked at the mean highest daily dose after conception in milligrams per kilo per day that these mothers used. In the prospective cohort, women who had a child without a major malformation, that mean highest dose was .86 milligrams per kilo per day compared to relatively similar dosages in mothers who had from the prospective groups who had a baby with a major malformation and in 28 babies, identified retrospectively who were malformed. There is really not much difference here, and if you look at the same data in another fashion, looking at various dosage increments, at a dose of less than a half a milligram

etc. As you look at these stratifications of dose, the absolute risk for malformation is really not any different, with the possible exception here where the data is extremely thin so that I would not suggest that using a lower dose of the drug is likely to be an effective strategy for reducing this problem.

In conclusion, I want to make several suggestions. First, body counts should not be the major criteria for public policy intervention. It is not crucial whether the number of malformed babies caused by Accutane is 62 or 1,000, and making public policy by counting bodies I think is unacceptable. I would suggest that a more appropriate major criteria for regulatory intervention in this case would be to look at the magnitude of the absolute risk for adverse outcomes. The environmental exposures that have absolute risks for adverse reproductive outcomes comparable to Accutane are basically thalidomide and rubella infection, and the public health approaches to controlling those two exposures are extensive. First, thalidomide is only available through the IND status, and second, we have a national compulsory immunization policy to control congenital rubella.

A reasonable conclusion is toward control of

not comparable to that of other environmental agents that pose comparable absolute risks for adverse reproductive outcomes, and my recommendation is that the policies ought to be comparable assuming that no one has any stronger ideas about what the criteria for potential intervention ought to be. Thank you.

DR. BERGFELD: Thank you. We will move on to our next guest speaker, Dr. Richard Miller, Associate Professor and Director, Division of Research, Department of Obstetrics and Gynecology, University of Rochester, School of Medicine and Dentistry. I understand that he is a Ph.D. pharmacologist toxicologist.

DR. MILLER: I thank you for the opportunity of addressing you all today. I come to you as a scientist, but also Director of our Teratology Information Consultation Service for the Rochester region. I was hoping to delay my comments until the end of the proceedings to know what everyone else was going to say, but I will speak now.

The concerns I would like to raise are really echoed, are in follow up to Ed Lammer's presentation, and this reflects what may be happening with thalidomide, and how strictly it is controlled. I

information, and also raise some other issues for your consideration in terms of the control of isotretinoin.

With thalidomide, we know that it is only available at Carval to women of reproductive age, and under very strict supervision. What does that mean? That means they have to be hospitalized, but in addition, they have to have informed consent, they must have weekly pregnancy testing before and throughout therapy, contraception before and throughout therapy and evidence of menstruation every 30 days to continue therapy. These might be considerations for the Committee to at least consider some, if not all of them, but at least some of them. The ones that I would like to emphasize especially is weekly pregnancy testing. Dr. Brent addressed that issue earlier in the morning, and I would like to expand on it because I think we are talking here about behavior modification. We are talking both about the physician but also especially the patient. You hand out a consent form to a patient, and a few weeks later, she has forgotten about it. What we need is the opportunity to reinforce that, even though we will detect pregnancy earlier, we are also introducing into that arena the opportunity for the physician or at least the nurse in the office

basis.

Further to that, it is probably important to include obstetrical or gynecologic follow up and consultation and it would seem quite useful to have that type of cooperation because of the reproductive risks that one is talking about here. The reason I raise the issue of methadone is that that has been a very useful program for continuing therapy in monitoring the patient. I am not sure it is directly applicable here, but weekly pregnancy testing would at least establish the type of rapport that may be necessary for the types of reproductive hazards we are concerned with in this population. thank you.

DR. BERGFELD: Thank you very much. We have on our agenda now to move into the series of discussion relating to the options for dealing with the problem. Dr. Carnot Evans is going to present other options and questions.

DR. EVANS: You are aware that the Agency has not yet taken a position on how Accutane should be treated based on the memorandum which is at our disposal. You also have heard that through the discussion of the problems associated with the use of this highly effective drug, Accutane, which has side

recommended that we remove it from the market. While there may be differences between us, and the assessment of the degree of risk involved, there is no question that fetal abnormalities continue to be reported with the use of this drug despite our best efforts. How do we solve this problem? What options do we have?

Basically, we have two options. We either remove the drug from the market, or we relabel it. There are positive and negative aspects to each course, and let me enumerate. The positive effect of removing Accutane from the market would be the elimination of the adverse effects due to the drug which are the source of our concern. The negative effects would include the unavailability of a highly effective and useful drug to which there currently is no substitute. Men and women who would use the drug responsibly would be denied its use.

Negative effects would also include the likelihood of an underground through which Accutane could be obtained, and we already know that Accutane can be prepared chemically without great difficulty. Another negative effect is potential use of retinol which is available over the counter, and which could easily fill the void left by Accutane if removed from

the market. Vitamin A tablets are available at any pharmacy on an over-the-counter basis. Would this product be effective in the treatment of recalcitrant cystic acne? Undoubtedly. Would it also be fetal toxic? Absolutely.

There are several labelling changes which could be employed to help solve our problem. The most stringent of these would be to relabel the drug so that it would be contraindicated in women of childbearing age. The positive effect of this would be to eliminate the use of the drug in the at-risk group while leaving it on the market for men and post-menopausal females. The negative aspects, of course, are that women who would use the drug responsibly would be denied its use. Furthermore, there is the likelihood that a patient, denied the use of such an effective drug, would seek it outside legitimate channels. A further labelling change that would be useful would be to contraindicate the drug in women of childbearing age until a negative pregnancy test is obtained. We found out today that this could be expanded so that a negative pregnancy test could be required more frequently, each month or each week to assure the patient and the physician alike that it was safe to take the drug.