FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PREGNANCY LABELING SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

8:10 a.m.

Wednesday, March 29, 2000

Crystals Ballroom
Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

ASSOCIATED REPORTERS OF WASHINGTON
1523 North Carolina Avenue, N.E.
Washington, D.C. 20002
(202) 543-4809

ATTENDEES

SUBCOMMITTEE MEMBERS:

MICHAEL F. GREENE, M.D., Chairman
Associate Professor of Obstetrics,
Gynecology and Reproductive Biology
Department of Obstetrics and Gynecology
Massachusetts General Hospital
Boston, Massachusetts 02114

SANDRA TITUS, PH.D., Acting Executive Secretary
Advisors and Consultants Staff, HFD-21
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ELIZABETH ANDREWS, PH.D., M.P.H.
Director
Worldwide Epidemiology
Glaxo Wellcome
5 Moore Drive, Box 13398
Research Triangle Park, North Carolina 27709-2298

ELIZABETH ANN CONOVER, M.S.
Coordinator
Nebraska Teratogen Information Service
Munroe Meyer Institute for Genetics
and Rehabilitation
University of Nebraska Medical Center
985440 Nebraska Medical Center, Room 2074
Omaha, Nebraska 68198-5440

CHRISTINA CHAMBERS, M.P.H.
Epidemiologist
California Teratogen Information Services
UCSD Medical Center
Department of Pediatrics
200 West Arbor Drive
San Diego, California 92103-8446

JANET DARDEN CRAGAN, M.D.
Division of Birth Defects and Genetics
Centers for Disease Control and Prevention
MS F45, 4770 Buford Highway, N.E.
Atlanta, Georgia 30341-3724

ATTENDEES (Continued)

SUBCOMMITTEE MEMBERS: (Continued)

MARY G. HAMMOND, M.D.
Reproductive Endocrinologist
Reproductive Consultants, PA
1053 Fearrington Post
Pittsboro, North Carolina 27312

JAMES A. LEMONS, M.D.
Professor of Pediatrics
Indiana University of Medicine
699 West Drive, Building RR208
Indianapolis, Indiana 46202

ALLEN MITCHELL, M.D.
Director
Slone Epidemiology Unit
Professor of Epidemiology and Pediatrics
Boston School of Public Health and Medicine
1371 Beacon Street
Brookline, Massachusetts 02446

KAREN ROSENE MONTELLA, M.D.
Department of Medicine
Women & Infants Hospital
101 Dudley Street
Providence, Rhode Island 02905

JULIA SCOTT, R.N., Consumer Representative
President
National Black Women's Health Project
600 Pennsylvania Avenue, S.E., Suite 310
Washington, D.C. 20003

SHEILA WEISS, PH.D.
Assistant Professor
University of Maryland
100 North Greene Street, 6th Floor
Baltimore, Maryland 21201

PATRICK WIER, M.D.
Group Director
Reproductive Toxicology
SmithKline Beecham Pharmaceuticals
709 Swedeland Road, Mc#UE0465
King of Prussia, Pennsylvania 19406

ATTENDEES (Continued)

SUBCOMMITTEE MEMBERS: (Continued)

KATHERINE L. WISNER, M.D.
Professor of Psychiatry and
Reproductive Biology
Director, Women's Mental Health Care Program
Case Western Reserve University
11400 Euclid Avenue
Triangle Building, Suite 280
Cleveland, Ohio 44106

NON-VOTING SUBCOMMITTEE CONSULTANTS:

JAN M. FRIEDMAN, M.D., PH.D.
Birth Defects and Genetic Diseases Branch
Centers for Disease Control
4770 Buford Highway, N.E.
Mail Stop F-45
Atlanta, Georgia 30341-3724

KEN LYONS JONES, M.D.
Professor of Pediatrics
Department of Pediatrics
Division of Dysmorphology and Teratology
University of California, San Diego
200 West Arbor Drive, #8446
San Diego, California 92103

SUSAN KING, M.D.
Division of Infectious Disease
The Hospital for Sick Children
555 University Avenue
Toronto, ON M5B 1X8 Canada

DONALD MATTISON, M.D.
Medical Director
Birth Defects Foundation
1275 Mamaroneck Avenue
White Plains, New York 10605

ATTENDEES (Continued)

NON-VOTING SUBCOMMITTEE CONSULTANTS: (Continued)

JAMES MILLS, PH.D.
Senior Investigator
National Institute of Child Health
and Development
National Institutes of Health
6100 Executive Boulevard, Room 7B-03
Bethesda, Maryland 20892

NANCY WADE, M.D., M.P.H.
Council of State and Territorial Epidemiologists
NYS Department of Health Aids Institute
Corning Tower, Empire State Plaza, Room 412
Albany, New York 12237

GUEST SPEAKERS:

LEWIS HOLMES, M.D.
Professor of Pediatrics
Massachusetts General Hospital
Genetics and Teratology Unit
Waren 801
32 Fruit Street
Boston, Massachusetts 02114-2696

PHILIP RHODES, PH.D.
National Center for HIV, STD, and Prevention
Division of HIV/AIDS Prevention
Center for Disease Control and Prevention
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

ROBERT SHARRAR, M.D.
Merck and Company, Inc.
Sentry Parkway West
P.O. Box 4, BLB-30
Building West, Mail Stop BLB-30
Blue Bell, Pennsylvania 19422

ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

HOLLI HAMILTON, M.D., M.P.H.
FLORENCE HOUN, M.D.
DIANNE KENNEDY, R.PH.
SANDRA KWEDER, M.D.
EVELYN RODRIGUEZ, M.D., M.P.H.

ALSO PRESENT:

DR. DAVID ERICKSON

C O N T E N T S

P R O C E E D I N G S

(8:10 a.m.)

DR. GREENE: Good morning. I'd like to reconvene the meeting please. I guess there were a few last-minute technical glitches but I think we have them mostly straightened out.

The meeting will continue and according to your agenda, there are welcome and opening remarks. I really don't have anything that I need to add before we get started. Dr. Kweder, do you?

DR. KWEDER: No.

DR. GREENE: No, okay. So, we can get started with the first speaker. Dr. Hamilton from the FDA, please.

DR. HAMILTON: Good morning. I'm going to speak a little bit about the nuts and bolts of the FDA because I'm imagining that most of you haven't written labels. Is that correct? So, maybe you'll get a little bit of an idea of where we're coming from because some of the regulatory aspects are not purely science or epidemiological, but I'm going to talk about monitoring drug risks in pregnancy, the regulatory aspects. So, bear with me.

It's a three-part speech. So, this is the overview. First, we're going to talk about drug labeling and our role. Next we're going to touch a little bit upon

the pregnancy section of drug labels, which is probably the aspect you're most familiar with. And then we're going to talk about how information is obtained for labeling. People are going in the direction of what we can do to approve this. I don't think I'm going to be touching on this a huge amount except for some of what's a done deal.

So, introduction to labeling. At the FDA we regulate drugs and biologic products. We monitor and regulate the investigation, development, and the marketing approval of drugs and the licensing of biologics.

We don't conduct clinical research. Other federal government agencies conduct clinical research. Our capabilities in this area are extremely limited.

We review data provided by sponsors of studies. The data we review is proprietary. What we review may not necessarily reflect what a consultant has seen or what's appeared in the literature. It may look a little different.

We have final vetting at the time of marketing to assure quality and integrity. We can have site monitors go out and visit sites and review things, and we can try to get into the database to look at it. Of course, we review a report which is submitted.

In addition, it provides the basis for market approval. We hope it provides useful data for medical

professionals. More and more people are reading the label themselves, but generally this is the group that for prescription drugs we focus on.

It's also the basis for market approval where we have the most ability to interact and negotiate and leverage. The commercial sponsor owns the label. It's a legal document, and as I said, it's a focal point for negotiations. This is at the point where we can arrange phase IV studies, commitment to phase IV studies.

Once marketed, the company has an obligation to report all safety data and toxicities, and that's a regulatory obligation which we'll delineate later and describe how it works.

Drugs obviously don't have indications for use in pregnancy. Typical indications, tonsillopharyngitis, urinary tract infection, pneumonia. They're approved for treatment of conditions listed under "Indications," and that's how the applications come in. Generally an NDA can come in with an indication. Efficacy supplements are submitted during the lifetime of the drug for other indications if data amasses and evidence for its efficacy accumulates.

We don't regulate the practice of medicine. We try to be very careful about that.

The pregnancy section. We're hoping to add

information. Currently it's more similar to geriatrics. Pediatrics is a couple years ahead of us on directions we hope to go in.

Now, as I said, it's the focal point for negotiations. This is at the point where we have the most interaction with the company that I think can be very fruitful for everyone.

The new drug applications and product licensing applications approval negotiations can involve committing to phase IV studies. This is where we view we would have more leverage, for instance, to submitting for pregnancy follow-up studies.

In addition, efficacy supplements for already approved drugs and biologics can establish impetus for updating safety sections. When people come in for an additional indication, just for instance, if they have pneumonia and they want to acquire a urinary tract infection indication, we can look at that label and say, well, you know, there's some safety stuff we've been looking at. Why don't you review this and we can incorporate this in the label too. So, it can occur during the lifetime, but as someone mentioned to me last night -- Bob Sharrar actually -- it costs $150,000 to do a new label?

DR. SHARRAR: That's what I've been told.

DR. HAMILTON: So, for every blip, they don't want to do it. So, we want to get it all together at once when we do a new label. It's not something they're going to do on a weekly basis. We'd like to organize it and we try to do this.

Now, in terms of opportunities for new data coming into the label, we have the AERS system, the Adverse Event Reporting System, which relies mostly on case reports, the spontaneous reports of MedWatch, which Dee Kennedy has been involved with for years. These are not without problems and particularly for our area of interest. But they have proved to be a very powerful tool in a few circumstances.

The literature is a possibility. That is kind of hard for us to do on our own, but people certainly submit paper NDAs from time to time to get drugs labeled.

And then there are epidemiologic studies. This is your expertise. I don't have to go into it here, but generally we like to review what someone is intending to do to see whether it would support what they're attempting to initiate on the label.

Now, post-marketing safety information, as I said, are spontaneous reports, and after approval, there are definite safety reporting requirements that we go through. Serious, unexpected reports -- it's a regulatory

definition -- must be received within 15 calendar days. It used to be 15 business days, but now it's 15 calendar days they should be received by the FDA for our review.

Other events are reported periodically, and that depends on what point in the time line the drug is at. Newer drugs require quarterly reporting for 3 years, and thereafter safety reports can be submitted annually. However, that's other events. Serious, unexpected, it's always 15 calendar days.

Now, serious, as I said, has a regulatory definition and this definition has changed in the past couple years. But death is a serious event. We believe that's true. Life-threatening events.

(Laughter.)

DR. HAMILTON: Well, it makes sense, right? Disability, congenital anomaly is a serious event, and that's certainly something that would fit in with registries and other things we're looking at here. And hospitalization, whether initial or prolonged. Malignancy used to be a serious event. It has now been taken off because it is thought more to fit in with some of the other items up there.

Now, unexpected. This is my favorite definition because it's perfect for us. It's just not in the current label. So, if you ever are wondering whether

the event is unexpected, all you have to do is get your current label and see whether it appears in the label, and if it doesn't and it's serious, it should come in to us within 15 calendar days.

Now, I'm preaching to the choir here. But obviously, the limitations of case reports are such there's no denominator. You cannot draw a rate, particularly since drug use patterns in the population are very, very difficult for us to determine on a population base level. Impossible. So, denominators are fraught with hazard.

This leaves us with a bias toward abnormal outcomes because no one ever sends us a MedWatch report that says the drug was great. They don't have to and we wouldn't want them to anyway. But the serious, unexpected and the abnormal events that are reported to them and everything, even if it's not -- sometimes you can see unusual things like had a funny thought in the morning on an adverse event report.

(Laughter.)

DR. HAMILTON: No, it's true. If it comes to the attention of the drug company, they kind of have to send it in.

There's clearly an uncertain value for common events. It becomes very hard for us to make much use out of them. The information is often incomplete and very,

very difficult to follow up. There may be contact information, and that's just fine. But when you try to follow up on it, it's very difficult.

Under-reporting is obviously problematic. If the association is not made between the exposure and the event, we're never going to hear about it. Knowledge, time, fear of reprisal. The system depends on someone contacting us and initiating the report.

When are they useful? Well, when there's a biologically plausible event. If we're kind of thinking this could happen and suddenly it comes across your desk on a form, then you're going to sit up and pay attention to that.

If there's a pattern suggested. If three unusual events occur within a certain time frame and it clicks, certainly that's going to be useful.

When you have simple case reports. I mean, most of the case reports are a very old person with multiple medical problems on multiple drugs. It's very, very hard to figure out what happened. Those are really not useful. But that's a huge number of the case reports.

When things like dosage, timing, and other exposures are known.

And obviously rechallenge and dechallenge. Now, with that, if you take the drug away and it goes away,

that's a good thing. If, for some reason, the person is rechallenged and the event appears again, that's pretty good evidence for incriminating the drug.

Getting back to the existing pregnancy section of the label, again this is probably the part where most of you have reviewed and seen it. It was first addressed by the regulations in 1979. The goal was to assist physicians in prescribing for pregnant women. It attempted to simplify risk/benefit information by providing a scale, which is a simple scale and employs the letter categories A, B, C, D, and X.

Currently you can see where A is, controlled studies in pregnancy. This constitutes less than 1 percent of the labels. Actually if you look at specific labels for what we would consider follow-up type studies in pregnancy, we could only come up with two labels that have changes in text that's not a system, reflecting follow-up data.

B is where animal studies show no risk or the human data are reassuring. Again, it depends on how one interprets "human data are reassuring" because the margins of assurance here are something that's subject to interpretation.

C is human data is lacking and animal studies are positive or not done. Now, that's 66 percent of existing labels. That suggests to me that that's a problem

because I can't believe that all drugs are a C.

D, human data show risk, and the benefit may outweigh the risk, but there's clearly risks involved. So, there we get into a situation where it has to be weighed.

X is animal or human data positive, no benefit.

Now, the lack of data hinders us here, and we have almost no information at all in the pre-marketing phase with respect to use of the drug in pregnant women. Pregnant women are excluded from clinical trials, and if in a trial a woman becomes pregnant, she's usually dropped out. She's often followed up, but this is not a common event, and it's not something people seek.

The only information sources at approval are animal data and post-marketing human data if the drug is approved overseas, so to speak. That's all that's going to be coming across our desk at the time of approval.

Now, as we mentioned, most products are therefore category C. There are no requirements to pursue this to change you out of category C. There's no incentives. So, this kind of ensures in the current system that C is going to rule. Animal findings are almost impossible to erase. They can be duplicated and there they are forever. Serious adverse events can only go one way, as I said. No one says the drug was great when we used it. All we end up with is more to the toxicity profile, and

that can be a very powerful addition because a handful of case reports can trigger findings that are going to appear in the label.

So, we end up with language such as "use only in pregnancy when the benefit outweighs the risk." One of the problems is we don't provide you with benefit or risk. We haven't explored the benefit and the risk information is limited.

Now, one of the things we have high hopes for is we can change the system and that's what we're working on now. We have a new model for pregnancy labeling we're pursuing. I think Sandy mentioned a bit of that.

We're hoping to move toward narrative text and away from categories that are so focused in that they collapse huge amounts of information into one letter that may not provide you with everything you need in order to interpret the data.

There's been a current shift in thinking about risk management, in that more information can be provided. The fact is in practicing medicine today, we are dealing with a risk/benefit situation. There's no situation that's not without risk or possibly not without benefit, and it has to be presented in a balanced fashion for people to make their own decisions.

We hope to improve the data. This would help

us tremendously in improving the labels.

This could be a big improvement for us. The post-marketing reporting regulations are being harmonized. We're going to be following suit with it. The International Council on Harmonization was published in the Federal Register of November 1996 with a guidance for clinical safety data management. We're now in the process of incorporating them to post-marketing regulations. It's taking time but it's being done.

What will be a big improvement is that the overall safety evaluation will be required to periodically and specifically address positive or negative experiences during pregnancy or lactation. I probably should have underlined "positive" in addition to "negative" because right now we really are not doing this, but this is now going to be regulatory.

Then we move on to once we get information, what are we going to do. Risk communication. This is a big area for us and a new area for us in terms of the sort of label we're going to have to write. What information belongs in the label?

Well, we believe certainly well-documented, serious adverse events belong in the label.

Prescribing information, and to the extent possible, we'd like to refine that prescribing information

for pregnant women to include PK and PD data and issues related to what would be helpful to people who need to give the drug to someone.

Then population based data providing an accurate measure of what we know about the product use, a measure of assurance, so to speak. Do we have limits of safety or evidence that suggests that the drug is a useful addition?

As I said, we're not a research agency. We review science, but we also have a public forum, an interaction where we make regulatory decisions. We strike a balance between speaking out too soon and waiting too long to speak. If we wait too long, risk progresses, benefit is not gotten. We violate public trust. If we speak out too soon, we don't want to be creating fear in a situation where it shouldn't exist or other unwanted consequences of providing scare to an issue.

Here, pregnancy and perinatal exposures. Because it is such a new field, there are special issues related to it. The pharmacology is, as we've said, often poorly understood. We need more information here.

There's no knowledge in this arena, which I've alluded to, which is the prescribing for pregnant women and breast feeding women. It's kind of sad that something as easy to do as figuring out whether the product appears in

the breast milk -- I think we have the capability for this. We don't have that in the label. Some of the other issues related to that are more complicated, but that certainly is easy to figure out.

The population exposed is special. And I thought of this last night. Not only is it a special population, it's a transient special population. People are not pregnant or breast feeding forever, although it seems that way. It seems that way to many people who have done it. But the fact is that the population in this phase of their life for a shorter period of time than many of the other special populations we're dealing with.

Rare events are difficult to detect, as you've all discussed yesterday. When something occurs 1 in 10,000, it may not be picked up immediately at birth, and it's got a long latency period, it's very difficult to figure it out.

Case reports. We discussed that. There tend to be a lot of issues related to that and they may not reflect common events. They're hard to pull together, and the data may not be so good.

Barriers to spontaneous reports may also increase as we progress. We don't know what's in the offing in terms of perception of reporting and privacy issues and things like that. Currently privacy issues with

spontaneous reports have not entered into the situation, but we can't be sure that that will be the case in the future.

We're hoping that we can move forward with good science to underlie our decisions.

Here is an area where we really want the most certainty, but we're given no data, and that's the dilemma we're sitting in now. So, we'd really like to come with ways to improve the information we receive in a reasonable measure. I think we have to move forward, and I don't think here we can let perfect be the enemy of the good. We have to improve the system.

We have to bring more data into our risk assessments. A label that has no information I think is a useless label.

We have to especially expand this as new drugs are developed.

We have to encourage new tools and engage stakeholders, including patients, in the discussion about how we can use this information and effectively communicate it.

Finally, I think moving toward plain language in labels would be a big improvement too. We have to have a label that's far more easy to intuit.

That's about all I have to say. I'd like to

see whether there are any questions. I've run under my time, so if you have any, please.

DR. HOLMES: Holli, when you referred to the adverse drug reaction reports, you said there have been times when they've been useful. I'd love to know an example.

(Laughter.)

DR. HAMILTON: No. The captopril issue I believe came out of spontaneous reports. Certainly many of the drug withdrawals and black boxes that have appeared have appeared from safety reports. So, these have been useful.

I think in this setting, it's not a perfect tool, but it's certainly better than nothing. It has brought things to our attention and it has had regulatory impact.

DR. MILLS: I was wondering if you'd like to amplify a little bit on your comment about putting in a narrative. Particularly, do you have any sense of the length of the narrative, and would it involve things like saying that we have an experience with 500 women, 10 of whom had kids with birth defects?

DR. HAMILTON: I don't have the slide with me, but actually we had made slides of the current text that occurs in labels. One is the acyclovir label and the other

is the rubella label. Those are the only experience we have with it to date.

We're looking into this issue. This becomes the difficulty with measure of assurance and providing complete information. How much do you include? We would welcome comments on this issue.

It becomes easier to do if the data is excellent obviously. Well, no, where there's a lot of uncertainty with respect to what you're reviewing, it's very difficult. As a matter of fact, we always go through this among ourselves. Hard data, hard situations make very, very poor labels because it's very difficult to say much about them. Whereas, if you have something more clear cut, if you have plausibility, if you believe the event, if it's well documented, if you can go back to your sources, obviously we all feel more comfortable with that. And we have to explore, with respect to what you said, what kind of language is useful further.

DR. FRIEDMAN: I wondered if you could answer for me a question that I've always wondered about. You mentioned in the beginning that much of the data that you're looking at or usually the data that you're looking at at the pre-marketing stage is proprietary.

DR. HAMILTON: It is.

DR. FRIEDMAN: I understand that and I

understand why it is in most cases.

But I don't understand why safety data is proprietary particularly with respect to pregnancy and particularly if you're going to have a label that says a physician is supposed to weigh the risks and the benefits, and all he can know about what you know is two words that are on the label.

DR. HAMILTON: Well, that's what I said. We don't have language reflecting that. I can't argue with your point. This is the existing system, and certainly it's in place for various reasons.

DR. FRIEDMAN: But what's the rationale of having proprietary safety information?

DR. HAMILTON: I don't know.

DR. KWEDER: The data itself and what the actual volumes of data -- or now it's on computer for us -- is proprietary. Once a product is approved, at least recent products that are approved, the FDA reviews of that data are not proprietary. They are available under Freedom of Information. I forget. It might be a rule of three. If we have more than three requests for a review and you can request a specific review, it will get put on the web. Like for example, if the animal data, the pharm/tox review is available, it is public information.

If the product is not approved, then it remains

proprietary, but once it's out there on the market.

Also, adverse event data, I think as most of you know, is publicly available data. Post-marketing adverse event data is always publicly available.

DR. FRIEDMAN: Yes. I'm not concerned about drugs that are not on the market.

DR. KWEDER: Right.

DR. FRIEDMAN: But if I have a patient in front of me, knowing that it's available through Freedom of Information doesn't really help.

DR. KWEDER: Right, exactly. It doesn't.

Our reviews are increasingly on the web and rapidly available. You can just pull them up for the most part. So, you could sit down at a terminal and pull it up.

DR. HAMILTON: And look at the safety section of the review.

MS. SCOTT: Much of what we've heard at this meeting, at least what I heard, has not included input from the patient. So, I'm very interested in your last conclusion engaging the stakeholders, including patients, in the discussion of the changing environment of risk management. I think most of what at least I have heard, there seems to be a leaning towards a way of collecting data without the consent of women. So, I'd like to know if you could share a little more maybe of what FDA is thinking

about in that last conclusion about the involvement of women in this whole --

DR. HAMILTON: Certainly the plain language in the label itself is generally written at the level of the health care professional. But I agree with you. I think that making information more attainable is going to be an important issue. It's something I don't think in this area we've gotten into entirely yet.

DR. LEMONS: I just had a minor comment related to the definition. I was struck by the proposed future assessment of benefit versus risk in terms of positive or negative findings being reported during pregnancy and lactation, and yet the whole mind set of the current pregnancy labeling, a positive result for both animal data and human data is a negative finding. So, just being consistent I guess on what positive means, it might be helpful.

DR. HAMILTON: It's the issue of margins of assurance. We'd like to be able to provide not just the risk, but in terms of if you have exposures, what potential benefit is. We have to start focusing on that end of the equation to help the prescriber. It's not just enough to say don't prescribe. You pointed out the problem and that's pretty much why you're here today. What information would be useful and how can we get it?

DR. MATTISON: The challenge, it seems to me -- and it has come up several times over the past day -- is decreasing uncertainty both for therapeutic impact and also for risk. The challenge seems to me to be a regulatory structure that doesn't allow you to create ways of either providing carrots or rewards for reducing uncertainty around both questions. I'm sure that you and your colleagues, both in the agency as well as others within the industry, have thought about ways of rewarding the reduction of uncertainty.

Mike, I don't know if this is the right time to talk about it or if we ought to leave it for our discussion later, but if we can't do it now, I'd like to come back to that at the end to think about how do we reward the reduction of uncertainty for both benefit and risk characterization.

DR. HAMILTON: We've talked about that internally and we have some ideas. Clearly that's going to be something that we're going to have to introduce. We would welcome your discussion of the issues because I really don't want to go over what has been discussed internally at the moment. But I think that because the products are manufactured by industry, we have to provide them with some incentives. The agency has had some models for this recently, and I can't say that we probably won't

try to base this initiative on some of the other models that you may be aware of because this is a cross-cutting team.

DR. HOLMES: I wanted to follow up on Jan's comment about not having access to the safety data. A couple years ago, we had a scare about whether dextromethorphan-containing cough medicines were a concern. The data that was available concerning human exposure was rather limited. So, an obvious point would be we'll go to some of the manufacturers and get some of the animal data to look at. That might flesh things out a bit.

Well, one of the quick responses by senior people in the Teratology Society was just call the company. Well, I tried that. You can't even get a human being on the phone, let alone someone who can make a decision. So, that isn't a realistic way to flesh it out.

It sounds like what you have could be a mechanism. So, when Beth Conover is trying to get answers, as the OTIS folks often are scrambling back to the animal data because the human data is not adequate, she needs to know where to call. If she has to get two friends to call as well to hit the magic three, so be it.

(Laughter.)

DR. HAMILTON: Yes.

DR. HOLMES: But we don't know how to do that

and that might be the kind of thing we could publish in a letter to the editor that says, if you're trying to get the animal data through the FDA system, this is the number you call. This is the way the system works, and this is the level you'd have to reach before you're going to get it. That would really be very helpful.

Is this something we should get from you?

DR. HAMILTON: We can talk about it.

My take on what you've just said is probably that it relates to something lying in different review divisions.

Well, for instance, that medicine is going to be over the counter. Is it not?

DR. HOLMES: Yes.

DR. HAMILTON: It may be under monograph if it's X number of years old. So, it's not like we are one person who is doing this who coordinates it for the agency. Being under monograph, being OTC, it's going to be in a different review division. This is maddening for people outside the agency, I understand.

DR. KWEDER: And us.

DR. HAMILTON: Yes, it can be. I didn't want to say that, but frankly it can be for us too.

(Laughter.)

DR. HAMILTON: Finding out where the

information sits.

DR. HOLMES: Sure. I think it would just help the folks that are out there that agree very much with what Jan said. Why in the world can't I get access to the stuff the company uses to say this is safe? Just a how-to, the phone numbers, and websites and so forth.

DR. HAMILTON: Actually I like the idea. We'll have to discuss it.

DR. GREENE: Dr. Kweder, you had your hand up. Did you have a comment or a question?

DR. KWEDER: Yes. I wanted to just revisit Julia Scott's comments about patients. We recognize that product labels are increasingly read by patients and available to patients. We also are well aware that in the current environment, risk management is usually a shared responsibility between clinicians and patients. So, both parties need to have information that's readily available to them.

The current structure of how information is made available -- Holli mentioned through package inserts. Those have historically been directed to physicians and should be I think for the most part. There is a section in the label that's called information for patients, but that's still written for physicians. It's, doctor, this is what we would advise you to tell your patient and here's

some sample language you might use to do that.

We are increasingly trying to work with companies to develop, in addition to or as part of professional labeling, something commonly called a patient package insert, which is part of professional labeling that uses text that is in lay language that might be perforated and torn off from a product label, copied by a commercial pharmacy to be used in the CVS or the Walgreen's handouts that are given out to patients about medicines. Where we've been successful is we've been successful because we've worked cooperatively with companies to do that.

There is a whole separate initiative that is beyond the scope of this discussion for a different kind of patient package insert. The term is used "medication guide," and a medication guide would be a patient package insert that FDA requires that companies distribute, ensure is distributed with the prescription. To implement a medication guide is extremely complicated because, as you know, in the current system the package insert, the label comes with -- if it's a bottle of 500, you get one. So, there aren't 50 of them to account for the 10 prescriptions that go with that bottle of 500. It basically would require a level of effort that goes way beyond what our current pharmacy and distribution system would make easy.

Because of that, the Congress has told the FDA

that we will not require medication guides for all medicines and, in fact, maybe 10 a year. To get that information out to patients is the responsibility of the pharmaceutical industry in cooperation with medical professionals and pharmacy professionals, and it's outside of the purview of FDA to require that except in very dire circumstances. That was a little over a year ago.

To my knowledge, we have yet to require formally one medication guide because the bar that has been set by the Congress is so high. So, that's one of the barriers that we face.

We have been successful with some companies. In my own section of the agency, we've been very successful, particularly in the antivirals area. Most of our antiviral agents, whether they're for the treatment of HIV or for the treatment of influenza, have perforated patient package inserts, and many of them are sold in unit-of-dose systems where it's like one prescription is one bulk and the label comes with it.

But we're very concerned about that and so we're trying to find creative ways to get that information in language that patients will understand and hopefully facilitate the pharmacy industry in getting that information available to patients. This will be one part of that.

Does that answer your question?

MS. SCOTT: Sadly it does in terms of the situation for today, but I think clearly until women are involved in this equation, I don't think we're going to have full information and full disclosure.

DR. KWEDER: Yes, we agree. I think that historically our experience in this whole area of pregnancy labeling is that there has not been a great deal of interest and participation among women's groups, some of the women's health groups, and we'd like to see that increase.

MS. CONOVER: Let me just add. I would say probably half of my patients who come to see me have read the label. So, the reality is that they've seen it and they're usually really alarmed by it. When I write materials back to health care providers, I always keep in mind, in fact, that the patient often sees it. So, it's phrased in a way that I think both of them will understand or find meaningful. It isn't actually all that difficult to do, and so kind of a good goal.

DR. KWEDER: Yes, I agree.

One of the things that we have to keep in mind is that there is increasing literature that teaches us that women perceive risk information very differently than men perceive it. They can read the same things have a very

different response to it. I've never seen any research in this area. It's probably out there, but I would wonder if pregnant women perceive it even more differently. So, we have to tend to that.

DR. GREENE: I'd like to ask one last question, and that is, to pursue a slide that you showed, you used the metaphor of a balance and how the FDA has to balance their responsibility to protect the public versus reacting too soon and frightening people.

Sometimes some clinicians feel that the FDA's major concern is with respect to their regulatory responsibility and not being perceived by the public or the Congress or anybody else as being "asleep at the regulatory switch," and that they're not as worried about the difficulties that clinicians have in providing care every day.

How do you make those judgments with respect to reacting too soon versus making life difficult for clinicians who are practicing who have limited options?

DR. HAMILTON: What a big question. I can't report to have been privy at all the big decisions, but I can tell you they're not made lightly. Clearly this is taken very seriously. We try to consider every one. It's not a small consideration. Not a small consideration.

Following the newspapers sometimes it scares me

because you read the same stories I do about the sequence of events.

DR. HOUN: I'll just add that we see risk-benefit and risk management as a very complicated area in which we have a role through our drug evaluation, our reviews and our labeling. We try to give the best information possible to physicians and patients. On the other hand, we know risk management is also in the realm of physicians, how they interpret disease with this patient, how the patient interprets risk and what conditions they're suffering from. It's very complicated. I would just echo that we don't take this lightly.

I think some of the agony in terms of the press showing that there's a lot of controversy in FDA with drugs that have toxicity is because there is this dichotomy of views of how best to do this, and I'm sure among this table, there are these varying views of how best to manage risk. We have that microcosm, plus we ask our advisors, such as you, for help in doing these things.

DR. GREENE: Thank you.

I think we're going to move on now to the next speaker. Dr. Sharrar, please.

DR. SHARRAR: Good morning. I have been asked by the FDA to talk about the experience that Merck and Company has had in the process of developing a pregnancy

registry and to give you a perspective from the viewpoint of the pharmaceutical industry. Now, I do not speak for the entire pharmaceutical industry. I only speak for Merck and Company, but I think many of the issues that I address are issues that will be of concern to them as well.

The first point I want to make is that we are interested in describing the safety profile of our products and of sharing that information with health care providers and with consumers so that our products can be used both safely and effectively. Now, that is a difficult process to do.

We prefer to distribute our information through the learned intermediary. That's the physician prescribing our drugs. And I was a little bit surprised by the difficulty some people have had in getting information from pharmaceutical companies. We do have a professional information department that you can contact and get all the information you want on our product that's in the published literature. If you contact a representative or me, we have to respond within package circular because the package circular is something that's established between the pharmaceutical company and the FDA and is the true document of the company. And that's what we have to respond to whenever we respond to a request.

I have been contacted by health care providers

for information that we have in our post-marketing surveillance database and we have shared that information with them. We have not shared that information with consumers because, as you know, these are very difficult issues and we want to make certain that the information is in fact interpreted properly.

Now, let's go on to the pregnancy registries. So far, Merck and Company has established four pregnancy registries on our own: our pregnancy registry for Varivax, which is our live attenuated varicella vaccine; pregnancy registries for Singulair, which is a drug for asthma; for Maxalt, which is a drug for migraine headaches; and for Vioxx, which is our recently marketed Cox-2 inhibitor, the anti-inflammatory drug.

We also are part of the PharmaResearch registry for HIV drugs where we monitor the adverse experiences or problems with our drug Crixivan, our protease inhibitor.

Now, there are two points I want to make about pregnancy registries before I actually begin my talk. One is that the pregnancy registry that we have established is not a static registry. It has evolved from the beginning and I expect that it will continue to evolve as we develop new techniques or new methods of looking at things.

The second point I want to emphasize is that the pregnancy registry that we established we established

to make it as consistent with our routine post-marketing surveillance activities as possible. This is not a special registry that requires a completely different department. This a registry that's part of our normal operating procedures.

Now, the registry that I'm going to focus in on this morning, though, is our pregnancy registry for Varivax. The reason I'm going to focus in on that is because that was the first registry that we developed. It was developed in conjunction with the Centers for Disease Control in Atlanta, Georgia and an advisory board. Two members that were on the initial advisory board, Jan Friedman and Janet Cragan, are here today.

And it's also the oldest pregnancy registry. It is the pregnancy registry that has served as the prototype for the additional registries that we have developed. We kind of pattern it on those.

The first question you have to ask is why are we interested in pregnancy registries. The reason is quite simple. Generally there is limited information available about the use of a drug or vaccine during pregnancy and its impact on the developing fetus or on the pregnancy itself before the drug gets licensed.

There are animal studies that are done. Unfortunately, the animal studies frequently involve higher

doses of the drug than what's normally prescribed for humans.

Secondly, many of the observations made in animal studies may not really be applicable to the human population.

Furthermore, from the perspective of a virus, because of species specificities for most viruses, animal models simply do not exist for the live attenuated viral vaccines that we market. Clinical trials are totally not helpful. We would never enroll a pregnant woman in a clinical trial, and if a woman became pregnant while she was in the clinical trial, she would be disqualified.

So, the only information that we really have available to us is information that we collect through the post-marketing surveillance activities. I'd like to describe them as nothing more than observational, descriptive epidemiologic studies, which means it has all the limitations of such study.

Now, there are two short-term objectives and two long-term objectives that we have.

First of all, in the short term the individual who manages our pregnancy registry is the individual identified as the responsible and knowledgeable person who knows what is known about exposure to the product during pregnancy. This individual is available to provide

information to assist both health care providers and patients make important decisions about the continuation of the pregnancy or the continued use of the drug during pregnancy. Now, that may not sound like much to you, but to identify an individual who's willing to assume that responsibility and to be assigned that responsibility is, in fact, a major breakthrough.

There are also two long-term objectives. One is we feel that pregnancy registries can help us assess if there are any common teratogenic effects from the product.

Now, I do not believe that pregnancy registries can be used to detect small increases in rare events. It's simply not going to happen.

I also don't think pregnancy registries are going to be effective in determining the long-term complications of drugs used in pregnancy in terms of growth and development. That's also not going to happen.

The information that we do get from pregnancy registries, though, should be helpful and ultimately should enable us to modify our package circular so that it is in fact more useful. Now, when package circulars get modified, it's a joint decision by the pharmaceutical companies and by the FDA, and the FDA has the final say.

Where does our data come from? Let's be realistic. It's post-marketing surveillance, and post-

marketing surveillance is an imperfect system. It is a spontaneous, passive, voluntary, incomplete reporting system. We only know about those adverse experiences or use during pregnancy that some health care provider or consumer wants to report to the company. Therefore, post-marketing surveillance, or pregnancy registries, will have all of the limitations of post-marketing surveillance which Holli alluded to in her talk. This is not active surveillance. This is active follow-up. The pregnancy registries are not active surveillance.

When I did public health work for the City of Philadelphia, we had an active surveillance program for measles, but we called the school nurses and selected pediatricians and asked them if they had seen a case in the previous week. That's active surveillance. This system is all passive.

Now, our pregnancy registries are different than the routine post-marketing surveillance activities.

First of all, we do have established enrollment criteria. If a person doesn't want to be in the registry, they're not in the registry.

Secondly, we distinguish prospective reports from retrospective reports.

Thirdly, we use but do not require informed consent. We would like to use informed consent because we

need informed consent to help us get long-term follow-up information, but that's not always easy to get. In fact, so far we've only been able to obtain informed consent from about 25 percent of the people where we've tried to get it. It's a very difficult process. We really feel that it's a process between the health care provider providing care and the patient receiving care.

Perhaps the most important thing, though, I don't even have in this slide. What really distinguishes a pregnancy registry is the specific, special, intensive follow-up procedures. So, it is a passive surveillance system that has active follow-up and that's what distinguishes the pregnancy registries for routine post-marketing surveillance.

Let's briefly talk about our enrollment criteria. First of all, in order for us to enroll a patient, we do want patient identifying information, and we do want provider identifying information. We need that information to get long-term follow-up. You cannot call a health care provider and say, can you get me some information on a patient with the initials of PS who got pregnant 6 months ago or who delivered a year ago. It simply is not going to happen.

We also like to have documented exposure to the drug within a specified time period, and normally that time

period means since the last menstrual period.

We also have focused in on only those reports that occur in the United States. I'm going to tell you it's very difficult to get follow-up information on international post-marketing reports. We have to get through subsidiaries. We have to go through translation problems. There are all sorts of confidentiality issues that are involved. The reporting practices are different. The reporting criteria are different. It simply is not worth the squeeze.

We have added to our pregnancy registry, though, Canada for Varivax because we do have an individual in our subsidiary who is interested in the problem and was interested in getting the necessary follow-up information that we have.

Now, where do we get our source of information? We only collect information from health care providers, and when a patient calls for information, we ask them for the name of their health care provider and try to communicate directly with them. This is a conscientious decision on our part. We like to work through an informed intermediary. We do send out a lot of information to the health care provider, and we want to make certain that that information gets translated properly and shared with the patient.

When a health care provider reports a case to us, we fax to him a number of things. First of all, we fax to him a statement that does, in fact, contain all of the known information about exposure to that product during pregnancy. It will include animal data. It will include reports that we have in the post-marketing environment. It includes a lot of medical information. We also fax out at the same time the questionnaire, both the initial questionnaire and the follow-up questionnaire so that the doctor sees what kind of information we are interested in collecting. We fax out a consent form and try to get the physician to complete it and return it to us. All of this information is again mailed out within a week and also the mailing contains a copy of the package insert so that we are in fact consistent with FDA regulations.

We do classify our reports into prospective reports, which are those reports where we learn about the exposure before the outcome of pregnancy is known. These prospective reports are the reports that we follow in the pregnancy registry to try and quantitate outcome results.

However, we also include in our pregnancy registry retrospective reports, which are defined as those reports where you learn about the exposure and outcome of pregnancy at the same time. The retrospective reports are not used for analyzing outcomes, but they are very useful

for identifying the type of congenital anomalies that might be associated with the product in general. If we see a cluster of an unusual congenital anomaly occurring, that's a signal to us where we may have to generate and perform some more formal epidemiologic study to evaluate. Retrospective reports are also important and they should not be ignored.

Again, as I said before, we do try to use consent forms. Although efforts are made to get signed consent forms to collect follow-up information from the patient and the newborn, signed consent forms are not required for the patient to be enrolled in the registry. Our consent forms specifically ask for permission to collect information on a child up to 2 years of age.

If the health care provider, however, is willing to provide the information to us without the signed informed consent, we do take it and put it into the registry if it meets our enrollment criteria. Again, as I'd like to emphasize, only 25 percent of those reports have we been able to get signed informed consent on.

The next question we had to try to address is a very practical question and that is do you maintain two separate databases or do you have one database. We elected that the pregnancy registry database is incorporated into the same database that's used for all reported adverse

experiences in the post-marketing environment. There is not a separate pregnancy registry database.

We have to periodically prepare what's called periodic safety update reports for regulatory agencies throughout the world and we want to make certain that those reports that we prepare and distribute do, in fact, contain all of the information we have on our products, which means that special information that we've obtained through post-marketing surveillance. You have to have one database so your data are consistent.

The next question that comes up is reporting to the FDA, and this is the philosophy that we have developed. Since these reports come in to us through the routine post-marketing surveillance environment, we consider them marketed reports and treat them so for reporting purposes. These are not special study reports. All congenital anomalies or serious, unexpected events of pregnancy associated with use of the drug are reported within 15 calendar days according to the FDA regulation. Exposure during pregnancy reports with non-serious events or serious expected events detected by follow-up questionnaire are reported to the FDA in the periodic reports that they receive. This means our pregnancy registries are consistent with FDA regulations.

You have to ask yourself one question too. If

you take a look at the criteria for study reports, it says that you have to be associated, unexpected, but who is going to determine if it's an associated? In a study report, you have an investigator who knows the patient, who knows the study, who knows the drug, who decides if it's a possibly associated event or not. Most pregnancy registries you're dealing with private docs who do not have that kind of background and information, and I can tell you the pharmaceutical companies do not want to be put in the place of deciding whether or not it's associated or non-associated. We will simply report all of those to the regulatory agencies.

Now, what about data collection analysis? I do think we have to be consistent. We have developed standardized questionnaires to collect information for specific exposures, and our questionnaires are one-page questionnaires and they are as simple as we can make them. They ask for demographic information. They ask for prior pregnancy histories. They'll ask for drug exposures, and they may ask about conditions of the disease. There's some variation depending upon the registry, but they're as consistent as we can make them.

We do not ask questions that we consider personal such as, why was the pregnancy terminated? Is the patient a smoker, an alcohol user, or a drug abuser? And

we do not ask the private physician to comment on causality.

The standard definitions we use to analyze the data are pretty much the same standard definitions that have been developed by the CDC and other experts in the field. We want to make certain that our reports are as consistent with other reports out there as possible.

The third point is we're forced to compare our outcomes with standard outcomes from the general population. We do not have the authority to collect information on patients not using our drugs. We can never come up with a control group. That has to be done by some outside agency, probably the CDC or some governmental agency that has the authority to collect such information.

We have tried to promote our pregnancy registries in different fashions. First of all, we have placed an announcement in our U.S. product circular in the Precautions Section under pregnancy, which reads as follows: "Merck and Company, Incorporated maintains a registry to monitor the pregnancy outcome of women exposed to drug, Varivax, while pregnant. Health care providers are encouraged to report any prenatal exposure to the Varivax by calling this 1-800 number." It's the same 1-800 number for all of our products, but that's how we announce it in the package circular.

We're in the process of preparing some journal articles, but you really can't prepare journal articles until you have some data to present.

We did announce the Varivax pregnancy registry in the MMWR when it was first started. There has been an article in the MMWR talking about product confusion where people received varicella vaccine in place of VZIG, which is what they should have received because they were exposed to chickenpox during pregnancy. And in that article, again we got more publicity about our thing.

We have, in the past, had some advertisements in professional journals. We talk about our pregnancy registry in various conferences. Our field representatives are taught when they detail the products that we have a pregnancy registry for to talk to the physicians about the fact that we have a pregnancy registry and about the fact they should report exposures to us from the patients using the drugs.

We're in the process of trying to develop a website that could be hyperlinked to other areas as well. That's not happened yet, but that's what we're trying to do.

As I said, we also had for the varicella pregnancy registry an advisory board. We used that advisory board, along with outside consultants to help us

evaluate certain congenital anomalies that have been reported to us. We also used the advisory board to review annual reports that we prepare and other manuscripts for publications or disseminations. We want to make certain that the interpretation we've given to our data is a reasonable interpretation that really is consistent with other people's interpretation as well.

It's interesting. We have not developed an advisory board for Maxalt and Singulair because so far we haven't had the need to. We are using the same format pregnancy registry for them. We've not identified any congenital anomaly that needs evaluating yet, so we really haven't established one.

In conclusion, I would just like to emphasize that pregnancy registries using post-marketing surveillance data can help provide useful information about exposure during pregnancy. Pregnancy registries must have formal enrollment criteria and standard definitions to interpret the data properly. We all have to realize that pregnancy registries are part of a passive surveillance system. It is not a formal epidemiologic study. It is a signal generator, and from the signals that are generated in the pregnancy registry, we could then develop more formal epidemiologic studies to evaluate the problems that we identify.

Thank you.

(Applause.)

DR. GREENE: Thank you.

Questions or comments for Dr. Sharrar, please? Lew?

DR. HOLMES: Let me just explain my comment about calling and not getting anyone. A registry is perfect. There's a phone number answered by someone who knows when the caller says I'm looking for more data. That's the connect you want.

What I was pursuing was dextromethorphan, which is an over-the-counter drug, that is included in products by a lot of companies. So, I simply called the drug information number listed in the PDR, and the person who answers the phone when you say, how do I get data on animal studies, has no idea what you're talking about. Of course, as I said, most of the time you get an answering machine, and when you finally get to someone, they then have to send you to someone else.

The point is if it's a counselor preparing for a patient visit a few days later, you're into a system that's too prolonged for this to come together for that particular discussion.

So, out of this frustration, the proposal was made that maybe OTIS could identify in many companies the

names of individuals whose phone number would be made available who would be identified so that these calls could be more successful in a timely way. I don't know that that happened. Did it, Beth?

MS. CONOVER: Actually, let me say of course when we complain, we're not usually complaining about Merck in terms of doing this.

In fact, it's true that one of the things about setting up a registry is it kind of changes the mind set I think within the company about the fact that you can expect to receive phone calls from people asking about reproductive outcomes.

Particularly with the smaller companies, but even with some of the bigger ones -- I called about a new drug used to prevent organ rejection in organ transplant people. The animal data on the label looked a little alarming and I was trying to find out if they had any human data at all. It took 3 hours, and I never really did get an answer. They had some human data. They wanted my data and they wanted me to give them some information. But I could never find someone who felt confident enough to talk to me about what had been reported, and they would say things to me like, well, we know you won't understand that this is retrospective data, and so we don't want you to be alarmed. So, then I really wondered what they had.

It just happened to be a day when I had had a couple cups of coffee and I dug my teeth into it. I really wanted to know what they knew, and I had to get very, very aggressive to get the information. As I say, in this particular case, I never did find someone who felt comfortable sharing that information.

Now, when there's a company that has a registry, even if I'm calling about a medication that's not a registry medication, there is frequently an identified person who is used to dealing with reproductive questions who I can start to talk to, to converse with about that information, and often much more readily available and not alluded to as -- in other situations, they'll say, well, somebody else -- I think they looked into this several months ago. They're not here. They're on vacation. We don't know what's in their computer. Some day we'll send you something. We get lots of answers like that, and pregnant women hate those answers. They want to know why a manufacturer who has this really sophisticated drug that's a wonderful cure for their problem can't pull up some information on the reproductive consequences. So, I can't tell you how much we appreciate manufacturers putting some time and energy into this.

DR. SHARRAR: I know it's not always easy to get information, and I don't pretend to say that it is.

And it's not always to get information from Merck either, although we do try.

I do think having an identified individual has been a major breakthrough for us because otherwise you might have gotten bounced around. I would like to just for a moment introduce the person who we work with at Merck who is head of our pregnancy registry. Her name is Kris Shields. Kris, would you stand for a moment?

Kris is a masters trained nurse who specialized in midwifery, and she also has a masters in epidemiology. So, she's well trained for the position that she's in and has done a remarkable job in helping us develop these registries. So, I want to publicly thank you, Kris.

DR. GREENE: Thank you, Dr. Sharrar. One more question. Then we'll move on. Yes, Don?

DR. MATTISON: Do you anticipate that the guidelines under ICH will improve collecting adverse event reports for internationally marketed drugs, which essentially are all of them, or for creating international registries? And if they don't, how should they be revised to enhance international data collection?

DR. SHARRAR: Well, I think the ICH efforts will improve reporting of adverse experiences associated with the drug. I think it's going to be a long process. There are real cultural differences from reporting in the

European community compared to reporting in the American community. I don't think they're going to be easy to overcome. I think it's going to improve the system.

I think we're getting better all the time. In fact, when I was in medical school, I was never taught to report any adverse experience to anybody. When I first started at Merck, we weren't getting many reports in either, but now I can see, in the last 5 or 6 years, the public and the professional people are taking an interest in post-marketing surveillance activities, and we're getting far more information than we ever did before. So, this is becoming a major issue and I think things are getting better.

DR. GREENE: Sandra, the last word.

DR. KWEDER: Yes. I just wanted to echo Beth Conover's comments and thank Merck and Glaxo and some of the other groups that are here who have put a lot of effort into this. One of the things that I've certainly experienced and others at this table, in trying to generate enthusiasm in data collection among companies over the past few years, is that there really is a large contingent of folks in the industry who are very anxious about this. They're very reluctant to put resources toward this and for a variety of reasons, and they're not all bad reasons. Some of them are good reasons. But I do hope that the

folks who are here at the table take this encouragement to heart and those companies that haven't taken measures like having a person within their safety group who really is dedicated to this and is there internal expert will begin to think about the long-term wisdom of doing that.

DR. SHARRAR: Thank you.

DR. GREENE: Thank you.

The next speaker is Dr. Lewis Holmes.

DR. HOLMES: I talked to Jan Cragan about how I was to interpret the title of my presentation and I interpret from our discussion that I should really talk about issues that relate to how pregnancy registry data might be put into the context of talking to patients. I know there are several people here who talk to patients, and so I'm representing that particular perspective.

I am bridging the old carrousel slide system with a new laptop system. This is sort of making Allen Mitchell not feel left out.

(Laughter.)

DR. HOLMES: So, first I wanted to discuss the point of you're about to see someone and you're trying to assess what the data is. There are obvious issues about the sources of information and for the discussion today, obviously one of the questions would be is there a pregnancy registry and what is the data.

The woman whom you're about to see is concerned about fetal effects. She doesn't come in the door saying, I only want to know about structural malformations, although that's obviously one of her major concerns, and usually effects on intelligence is another one of the major unspoken priorities.

So, when you're going through the data, you're looking at study design. If you have the time to read the study, how was it done, obvious bias issues, obvious issues about whether they were controlled or not, an adequate control group.

What I'd like to emphasize today are, since this point hasn't come out yet, some of the clinical points that you'd make as you looked at the data that had been collected. The next few slides will go through process.

So, point number one. If you looked at the data, this is the data that's included in the packet from the New England Journal of Medicine paper where we summarized the data on this surveillance project at Brigham and Women's. When you pull together all malformations, did the person separate out things with obviously other causes like chromosome abnormalities or single mutant genes? So, were the obvious genetic disorders removed?

Birthmarks. One of the things I make a point about is that you shouldn't include as a malformation

birthmarks. Here is something that the parents with young children in the audience will recognize immediately, these common capillary hemangiomas are so common in about at least half of infants. Some reports, unfortunately, list these and that's totally worthless.

Or is it something like this? And if so, is that a structural malformation? It's clearly a vascular abnormality. But you want to look at the data set and see what they've lumped into that numerator. I argue that birthmarks are really a separate issue and shouldn't be in there.

Well, club foot is an example of something that often conjures up being significant medically. Yet, these calcaneovalgus foot deformities, which are usually positional, is that really a major outcome? Is that a structural abnormality that you'd want to note the presence of in the numerator? I would argue that positional deformities should not. Sure, if it's a major club foot deformity, you could make the observation that's significant. You could also make the argument it's really a deformation and not a malformation.

Webbing between the second and third toes is a good illustration of common minor anomalies. Do they really belong in the numerator? I don't think so and yet a lot of studies will have them.

Well, just to pick an example, this goes back -- I believe, Allen, you were part of this authorship back when you were much younger, 1973.

(Laughter.)

DR. HOLMES: Back in his early days. You can see the investigators were studying diphenylhydantoin work and they were looking at different periods of exposure. This is the National Collaborative Perinatal Project data. We don't need to dwell on that.

But the point is are all of these things that you would agree are really major structural abnormalities? One is a size issue, microcephaly. The syndactyly. I think there was concern about whether those were syndactyly, toes 2-3. Cleft gum. Now we know to be suspicious of VSDs. VSDs are extremely common and many studies are now excluding the muscular type of VSD as not something that's appropriate to list as a major outcome.

Now that most women have ultrasound during pregnancy, lots of anxiety and tears are generated by finding a variety of anatomic variance during pregnancy that find their way into the numerators of studies reporting the frequency of "abnormalities." I would argue that this is a separate category and really shouldn't be in there.

So, in summary, what I'm making a pitch for is

if you're going to cite a study, you'd like to see in it that the folks who designed it had established what their inclusion criteria were, what the outcomes were they were going to look for, and what they were going to exclude. And if they didn't do a good job of that, that's something you've got to pay attention to as you prepare to use this data.

The larger point is this woman wants to know about effects during pregnancy. There's a wide range of potential environmental effects, only some of which are the malformations that get all the attention. So, one of the major points that you've got to present up front is some aspects of this exposure have been studied and some have not. Usually most have not been looked for.

So, now we can switch to the new kinds of slides.

So, in summary, you do your homework beforehand, and what I do is counseling on a one-on-one basis. Beth obviously represents a group of people who do this over the phone. But all people try to prepare, spend some time looking at the sources, and what I'm arguing is there should be a very active process of making value judgments about the quality of the information you've got, recognizing that most studies only address certain outcomes from an exposure and very few have had the full extent of

outcomes looked for.

So, when you get to the process itself, I set aside an hour for this, and that's a luxury. That's why the OTIS system developed because there are lots of folks that don't want to come in and spend an hour doing this, and you reach a larger audience if you do telephone discussions. But Beth can probably tell me that there are many times she talks for an hour on the phone.

Key issues about this discussion. We've already talked about having the data that's available together.

Next step. You want to have all the critical people there. If you spend an hour talking to a woman, and her partner, her spouse, or whatever is going to be equally involved in the decision process, she ends up turning around and giving a 3-minute summary of what you spent an hour doing. So, it's much better if you can get the key people there. Sometimes it's grandparents to be. Sometimes it's a mother-in-law. Obviously this is a tortuous process to decide who should be there in a positive way versus who, by being there, will be totally destructive to the process. So, this is delicate, and you often know more after the session is over than you did before, and if you knew what you knew after it was over, you would have structured it differently. But crucial.

The other point is she's usually been given some information already. So, one of the things I try to do early on in the discussion is find out what the obstetrician's comment was. Maybe it was the obstetrician's nurse. Maybe the obstetrician's secretary took the PDR off the shelf, opened it up, showed it to her, read it to her. So, she comes in polarized and terrified by the inadequacies of the PDR. We refer to a lot of our consults as PDR-generated discussions. They wouldn't happen if you had decent data.

Then one of the larger issues that the counselor has to address and struggle with is what level of discussion is appropriate. You have women who come in with their Internet printouts that have problems with too much information. You have folks who come in with reprints that are all hung up on what does this mean, what does that mean. So, you have folks that want to go through the details and dot the I's and discuss study design and why you can't use this paper to resolve their issues and so forth. That's one group. And person-to-person counseling tends to attract those people because that's what they really want to do.

But there's also a group of people who haven't done that, and they're coming maybe because their doctor wants them to come. You say, why are you here, and they

are honest. They say, I'm not sure.

So, you really have to have some strategizing going on as you start the process. I find, as you begin to just get the history, when did the conception occur, what medication was she on, family history, so forth, that 15 or 20 minutes allows you to get your own sense of what level of discussion is appropriate here. Usually during that time, the reprints come out and the other stuff where you see the stack of printouts and you know where you are.

Now, I represent the AED Pregnancy Registry in this discussion and so I'll use anticonvulsant drugs as my example. If you're going through a discussion of anticonvulsant drugs, you not only go through what's known about the apparent risk and the limitations of the studies that have been done, but you really need to put together a game plan for her, at least a set of options for her.

In the case of the anticonvulsant drugs, you're trying to get her connected with her doctor in terms of what she can do. One of the things that I find has been helpful over the years in talking to women on seizure meds is to say, a lot of women in your situation, having heard the concern about, says, a doubling a risk for major malformations, are sitting there thinking, I'm going to go off that medication and nobody is going to know. If you say that, she'll sometimes smile and say, yes, I've already

made that plan or will not respond. But talk about the need for her to work with people, not to go out on her own to do stuff just because of the thought that she might damage her child by something she does and she'd feel guilty forever if that occurred.

Obviously, her doctor has to be engaged in this process too. Now, the doctor is obviously not going be there, and sometimes it's helpful for us to let him or her know what we decided. But get her and her partner who's there with her engaged in the whole idea of dose. We don't have data on anticonvulsants that speaks to the risk from this dose versus that dose, but that dose matters, and the lower the dose, the better. And a dialogue between her and her doctor and consideration of what her blood levels are over time during pregnancy is a very realistic way for her to channel her concerns and the discussions of her options.

Another issue that I think really takes her back to her obstetrician to talk about is that she's got to be realistic about what kind of reassurance she can get during pregnancy. There are the obvious issues of some women think unrealistically that amniocentesis is going to help when their taking a medication, but nowadays most of the focus is on sonography. Yes, there's excellent equipment and there are excellent sonographers, but a lot of the things she has questions about are not going to be

resolved even if she has ultrasound more often than she should. I tell them they're far more likely, if they have too much ultrasound, to stumble into an anatomic variance, and that's just going to drive their anxiety to the ceiling even more.

And then finally, for folks whose child has a specific issue, you can say, well, there are folks who can do exams at birth to help you settle whether this exposure during this pregnancy was a problem. Let me just give you an example.

Joan Stoler, who works on alcohol exposure in pregnancy, showed very convincingly that at a Boston hospital the children with signs of fetal alcohol syndrome weren't diagnosed by busy pediatricians who were doing what they were going to do. A study exam identified something that was passed by. The same would be true for anticonvulsants. The same would be true for a lot of exposures that have subtle effects that not every pediatrician is well prepared to look for and be discriminating and say, yes, it's there and or no it's not. So, there is a time when this would be appropriate.

So, you had the discussion that you think is at the level of complexity that makes the most sense. That's one philosophy. There are others who are taught or who are required to tell the patient everything. That's a

different style of counseling. I don't think it's good, but there are a lot of folks who are told, tell the patient about the animal studies at high doses even though it's not relevant, and I think that creates more problems than it solves. You've had that discussion.

To me the key is communicate with her. Write it down. Make it short and sweet, a page, page and a half hopefully. Send it to her. A copy goes to her care providers. As you might guess there are times when the woman is really quite upset. Issues are complicated and follow-up phone calls are appropriate. Other times it's pretty routine and you feel that that's really not necessary. I find in the setting where I am rarely do we actually meet again. There are exceptions obviously to that.

But generally this to me is how the process ties together. It's a luxury when you're doing it person to person. It's a luxury when you can do it for an hour. But I think in the best of worlds that's the way it should be done.

Let me stop there and see if there are any questions.

DR. GREENE: Yes, please.

DR. WISNER: There are times when your discussion with the patient might lead her to prefer a

particular treatment plan that the implementing physician does not approve of or perhaps they've had legal difficulties with a similar plan in the past. I am curious about how you try to resolve those kinds of difficulties.

DR. HOLMES: You would predict this is not easy. Sometimes women come from care providers who are opposed to some of the options. Let's say a woman has an exposure to something -- and I won't use names to avoid the problems that go with that -- that has a high risk for serious abnormalities, and they, hearing the information, decide they want to terminate the pregnancy and their care provider says, I won't support that.

This usually means that we ask her to talk to someone else, typically a social worker. It's the awkward process of deciding whether she wants to stay with her care provider or go to someone else and pursue her options that way. Obviously, you try to resolve it in the context of her health care system and you're not trying to stir up trouble. You're simply trying to help her follow what she wants to do.

One of the other problems you get into is the bias, the preconceived notions of the person who sent her in the first place. I'm convinced that medical care specialties talk only to each other and there is rarely cross-fertilization. I mean, psychiatrists listen to

psychiatrists, neurologists to neurologists. If you're not in that club, your credibility is less and your chance of talking to them is less. So, a lot of the work on anticonvulsants has been discussed a lot by neurologists. The same drugs are now being used for psychiatric disease and it's as if it's a new beginning. These previous discussions didn't happen.

So, I've been referred more than once by a psychiatrist a woman who is on lithium which psychiatrists are taught to go to your grave before you ever let a patient of yours on lithium get pregnant. So, she wants to get pregnant. She's on lithium. Which should I put her on? Tegretol or Depakote?

(Laughter.)

DR. HOLMES: You can tell from the chuckles of the group up here, this is a major discussion process not only for her, but the person who sent her clearly is not up-to-date on the information on lithium, Tegretol, and valproic.

DR. WISNER: Just as a follow-up to that, it seems to me that we have this risk-benefit assessment and we focus that on the patient. But in fact, what you just described was almost a parallel risk-benefit process that the care provider has to make as well. If that doesn't match the patient's, then perhaps a different care provider

is appropriate.

DR. HOLMES: Yes, Beth.

MS. CONOVER: In the best of worlds and again when I've had a big cup of coffee, I almost always -- I see actually a lot of patients directly for counseling --

DR. HOLMES: Oh, good.

MS. CONOVER: -- and even more than an hour sometimes. But it is a luxury and sometimes patients can't get to us in person anyway.

But I almost always talk with the prescribing physician. I'm lucky. I am a genetic counselor. I can't prescribe. Dr. Holmes can, so he might be in a different situation. But I'm not the prescribing physician.

I think it's really important for me to talk to them ahead of time and get a better sense of what they see as the available options in medications because I'm not the one that would know what would treat their seizure disorder or even their depression, the things they have already tried, or the things that they see are appropriate. So, part of my thought process, before I ever talk to the patient, is what the physician has already gone through in deciding that. Then I let them know up front what I think I'm going to be discussing in the session and the options I'll be offering the patient that are congruent with what the physician sees too.

Now, once in a while you get a physician who's really way off base, but most of them aren't referring to Dr. Holmes or me actually to begin with. I think it's the ones that don't refer to us that are more likely out there. They're really happy to see that information up front so that they're not caught flat-footed or whatever not knowing what their patient knows. So, I think in genetics we're really careful about communicating with the person who has the full responsibility for treating the patient.

DR. HOLMES: One of the things I try to do is use that as an opportunity to send them the title page from Jan's book and say here's an example of something that costs about $80 or $90, something like that, that gives you editorial comments about the risks of this particular drug because most doctors don't know that the PDR is woefully inadequate, inaccurate and don't have an alternative. So, I don't have any financial interests in Jan's book, but it allows you to say here's something your emergency room ought to have. Put the PDR away. That's not the way to do this. And that's sort of your educational window. I'm not sure how successful it is.

DR. MONTELLA: I find the other thing that works a lot, because I end up in the exact same situation, is talking to the physician afterwards. I always call the care provider after I've seen the patient. Rather than

say, listen, buddy, this is what's going to work, you're wrong, I often say, boy, the patient is worried about this or that and I'm trying to weigh and I know you think that is best for your and what the patient is saying to me and put it from the patient's perspective, that they may have a question about this that they're too uncomfortable with that. What do they think about doing this or that? Or the patient has heard from their mother or their uncle or somebody, and that will usually work, as long as you aren't going at somebody and making them defensive. That's what I do afterwards.

DR. HOLMES: Yes. I think the other thing we need to think about is where is this business going and what will happen next. We know there are several drugs where the molecular susceptibility issue is on the table as a concern, and we aren't there yet. So, we don't have to put in our conversations a discussion of whether you are intrinsically a high risk person or intrinsically a low risk person. But when that happens, it's going to make this whole counseling process much more complicated and probably more expensive and polarizing, those who can have the tests versus those that are going to have to say I can't do that.

DR. GREENE: Ken, did you have a question?

DR. JONES: Yes. Lew, you sort of represent --

not sort of -- you represent this AED registry and Bob, who talked just before you, represents the Varivax registry. You really presented one way to counsel relative to the anticonvulsants and how you do that when a woman, I assume, contacts you through the AED registry.

DR. HOLMES: No, no. This is totally separate from the registry.

DR. JONES: Okay. What I was wondering was, do you perceive this kind of counseling to have anything to do with a pregnancy registry?

DR. HOLMES: No.

DR. JONES: No.

DR. HOLMES: No. This is one of the things early on that we had to try to be as explicit as we could about because we get a lot of calls from people looking for information. We have a one-page summary that I think everybody in this room would probably agree with in terms of see if you need to be on any medication in the first place. If you're on two drugs, can you be on one? Talk to your doctor. Keep the dose as low as you can. Take your multi-vitamins and folic acid and so forth. That we provide to those that want it and basically ask them to work with their doctors if they want to discuss with someone what I just showed you.

The AED pregnancy registry is a North American

registry just like Bob's Varivax registry is. So, you really have to put them in connection with folks in their area. If they say, well, who do I call, usually telling them to go back to their doctor is enough to start the process locally where they know the resources. Occasionally we might offer them the names of an OTIS center in the region or whatever.

But I think registries are really different. Registries are post-marketing surveillance where you are trying to get together data. The way the registries that have been described differ -- I haven't really described how the AED pregnancy registry works, but you can tell from my previous comments we're talking about collecting information from the care providers. We're talking about interviewing the mother. You're hearing two different models, but that's still just collecting data. That's not counseling. Very different.

DR. GREENE: Dr. Wisner?

DR. WISNER: I have two questions. The first is whether in your feedback to the patient, you use any specific structure perhaps around reproductive toxic domains or whether it's more of an open discussion related to the specific drugs that are relevant.

The second question is how you deal with areas in which there's no information. In other words, how do

you talk to the patient about no data so that they can begin to assign a value to no data in their decision making process?

DR. HOLMES: Well, it would relate probably well to an e-mail I got a couple of days ago from a counselor whose patient is asking about a new anticonvulsant for which there's no data yet. She said, should I discuss the findings from all the other anticonvulsants? My answer back was, you really can't do that. You've got to treat each one separately, and if you think about the anticonvulsants currently on the market, they're quite different in terms of their fetal effects both in terms of the magnitude and the type. But I think it's really hard.

When I'm talking to a patient about an exposure where there's no data -- let's pick someone with a panic attack, so they're highly motivated and they come into your office and they've got lots of printouts from lots of people and their brain is moving pretty fast and they're peppering you with questions.

I say there are different levels of information. There's this circumstantial data that says when I go to meetings or I read journals, there are reports of concern that drug X is associated with this problem. That's sort of the first flag that's waved. Then the

second would be, say, an abstract at a meeting or something where someone has done a small pilot to try to say there seems to be something here or there isn't. And then a much different level would be these big studies like the studies done of Prozac to try to settle whether there's an issue here or not because the drugs are in use so much.

And I go through that and say there are different levels of information and say, at this point the medication you're asking about hasn't gotten into that process yet to my knowledge. Now, some people find that helpful, some don't. But that's about all you can do is describe the process.

Most women I don't think realize that drugs get on the market without having had any data obtained from human pregnancies. They just can't believe that.

DR. GREENE: Most doctors don't know that.

Jim?

DR. MILLS: I'm not a geneticist, but I get to field a lot of calls coming in to NIH about these sorts of issues. Jan's book and Tony Scialli's book and Tom Shepard's book are all very helpful for me.

In the first part of your talk, where you talked about things like capillary hemangiomas and things, I find that there seems to be a lot less available in the sense that -- David Smith's or the AASE book or something

like that are somewhat helpful. But I don't know of a lot of references that discuss the sorts of issues you're talking about in any detail, such as what does polydactyly mean for most instances. I'd like to give you an opportunity to suggest some references or some other sources of information for that kind of question, or maybe to write the book yourself if you are so inclined.

(Laughter.)

DR. HOLMES: I think one of the things that this raises is you theoretically spend a lot of time on the phone providing a lot of stuff that's not readily available. I think the issue of tell me more about this problem is a major thing all of us are asked about, and it isn't easy to come up with one thing. So, if it's a birthmark question, I usually have certain references for that. Polydactyly is probably an example of something where most of the books sort of pass that by because it is so common and don't discuss it. Ken's book that he edits is an excellent resource. Birthmarks are usually covered in things that are more geared for dermatologists. The Stevenson, Hall and Goodman book is excellent on common malformations. That one in particular is not only heavy but with that, it's expensive and a lot of folks are reluctant to buy it because they are afraid it will walk. So, there are a lot of resources, but there isn't any one

thing to recommend.

DR. GREENE: Allen, I think you had a question.

DR. MITCHELL: Yes. Lew, where epidemiology and clinical practice intersect and where the labeling issues also become critical, it seems, are how to tease out the notion of baseline risk from etiologic fraction or attributable risk, or whatever you want to call it. And simply put, if the risk of a cleft is doubled under circumstances where a drug is given and a woman winds up having a cleft, how does she know whether it's due to the drug or her baseline risk? Now, obviously she doesn't. But how do you deal with those issues? Because it seems to me that's not only a clinically relevant issue but the label ought to try to speak to that principle as well.

DR. HOLMES: If we put registries in the right perspective, you'd say you're going to have to hold the follow-up meeting in 10 years, assuming the registries start now, so that you could really have good data not just on all malformations, but specific outcomes like clefts. Given that the registries haven't been around long enough and the epidemiologic studies aren't big enough to address specific major malformations, I think you're really stuck. You're ending up with a personal opinion.

As Ken has said very eloquently not only here but other places, drugs that are teratogenic should be

expected to produce a distinctive pattern of effects, and you would assume that if a child has a cleft palate from an exposure, the sensitized pediatrician or dysmorphologist would, in examining that child, tell you, this is not just cleft palate, it's this, this, this, this, subtle, minor, but there's a whole constellation of things here.

Certainly anticonvulsants would be a good illustration of this. The frequency of the anticonvulsant face, depending on your definition, is anywhere from 10 to 15 percent. The digit hypoplasia is 5 percent. Those are the dominant background findings. The major malformations are 4 percent. So, most of the exposed children with these distinctive phenotypic effects have no major malformations.

So, until the studies are done, the answer to your question is simply going to be personal opinion. How do we know? We don't know. But once the studies have gone on long enough, then you'd hope that these offshoot studies get done so that someone can say, all right, here in this registry X number of children were identified with major malformations. We did a separate study with a blind examiner, exposed with major malformations, without, and we showed for the first time there is a distinctive pattern or there isn't. That hasn't happened. Whether there will be funds to make it happen, who knows? But until then you're just left looking at the ceiling and saying, I think it is

or isn't causally related.

This is the problem with the adverse drug reaction reports.

DR. GREENE: Don, did you have a question?

DR. MATTISON: Yes.

MS. CONOVER: I think what you were alluding to and it's so intuitive for us in genetics, as I bet it is for you, is that any increase in risk always needs to be phrased in terms of your background risk regardless of what kind of issue you're discussing. But perhaps that is really an important issue for labeling, which is that patients always need to be reminded of their background risk. Again, I talk to residents about discussing exposures as what this has done to your background risk, what this is adding to it or whatever. It needs to be very clearly phrased. It's important for the patient. It's important for liability. It's important for our research.

DR. MATTISON: In preparing for counseling and in doing it over the number of years that you've had the opportunity to develop your experience, you've had a chance to look at case reports, epidemiological studies, animal studies, and synthesized information. As you think about the kinds of materials that are available and the way that you use them, how would you structure information collection and synthesis in a way that might make it easier

both for you and for other counselors, other health professionals to provide advice to families?

And then how do you think about translating that in language that might be comfortable for the diverse populations that we're going to have to be counseling with very different value systems? Again, maybe we need to hold this?

DR. HOLMES: Would you rather hold it till another time, Mike?

DR. GREENE: Yes. We are running a bit late. So, why don't we take our break and we'll come back to this in the general discussion. We stand adjourned for 30 minutes.

(Recess.)

DR. GREENE: I'd like to call the meeting back to order.

The next speaker of the morning will be Dr. Philip Rhodes from the Centers for Disease Control. Please.

DR. RHODES: Good morning. Thank you.

This morning I'd like to talk about the role of surveillance and possibly compare and contrast the role of surveillance registries and epidemiologic studies. I'm not going to give you firm definitions that you'll always know whether something is surveillance or registry or an epi

study. I hope I can blur the lines and also draw some distinctions at the same time.

Just a quick outline of what I'd like to talk about this morning. I'd like to give you a little sense of what my background is at the CDC in terms of surveillance systems, registries, and various epi studies. Talk about some general and important surveillance issues. Give some specific examples of things that I've been involved in, and then try to tie them back to the workshop issues, as I've seen them in the book. Actually, as I go through the specific examples, I hope that you'll actually see a lot of the workshop issues brought out in those specific examples.

I've been at the Centers for Disease Control for longer than I care to admit sometimes. I've worked on a variety of projects, including the Agent Orange project, injury prevention, immunization program, STDs, and now HIV/AIDS. In all these areas, there has been opportunity to work on various surveillance systems, registries, and epi type studies.

Some various ideas and dimensions that I'd like you to keep in mind as I go through here is the incredibly crucial role of background information in doing any of these activities and also the idea that my results can be your background information and that your results then can be somebody else's background information in planning a

further surveillance system, starting another registry, doing another epi study.

Also, the important role of infrastructure, that things do build on each other, I think as we'll talk about, that surveillance systems do provide the infrastructure to do epi studies. Sometimes epi studies ironically provide the infrastructure to do surveillance.

Time is an important component, that you don't build infrastructure this week to do a study next week. These things take time to do. They take time to bring to fruition, and sometimes it takes time just to accumulate the amount of data that you need to draw your conclusions.

Also, the theme there is always more than one way to do what you're trying to do, and don't let the perfect be the enemy of the good.

Work with what you have. A study here, a study there. You might actually find out something eventually.

What is surveillance? Well, surveillance is obviously one of the central roles of the Centers for Disease Control. But surveillance doesn't mean that we just like to sit around and watch. Steve Thacker, who has played an important role in many surveillance systems, noted that at least public health surveillance is the ongoing systematic collection, analysis, and interpretation of data for use in the planning of public health practice.

Note here he talks about outcome-specific data, and that classically was the role of most surveillance systems, especially in regards to infectious diseases. But I think you can see that that quote is from 1988, and certainly since then, other types of surveillance systems have become very important, especially behavior related systems.

Alex Langmuir, essentially the father of surveillance at CDC, discussed the tendency of epidemiologists to equate surveillance with almost all of epidemiology and to blur the lines between surveillance and research.

Steve Thacker again tried to draw the line so that there were some boundaries in that surveillance in his mind does not encompass epi research.

However, surveillance has many purposes, as noted again by Dr. Thacker. A lot of these things are contained in a book, which I find very useful, edited by Steven Teutsch and Elliott Churchill, the Practice of Public Health Surveillance, an excellent book.

Surveillance systems have been used for all manner of things, obviously to portray the natural history of the HIV/AIDS epidemic, to detect epidemics, Hantavirus, other epidemics, even test hypotheses, evaluate, monitor changes in infectious agents, obviously drug resistance in gonorrhea, HIV, all manner of activities.

Dr. Teutsch emphasized there are certain activities that take place in a surveillance system, very importantly the case definition. I think we have heard some allusion to here, what are malformations. What one person views as a malformation is not necessarily what another person views it as.

Data collection is a very important aspect obviously. At various points in my career, I've had people tell me that data is not collected, data is produced. Data production is always an active role, and also then who is involved in that data collection is very important from the point of view of how much standardization can there be in that data collection. When data collection takes place in many varied locations, like in 65 programs as it does in HIV/AIDS, it becomes very difficult to standardize that data collection compared to, say, collecting data at 3 sites for an epi study.

We've heard some talk about active versus passive systems. That is certainly a very important concept. Sitting around waiting for forms to roll in is very different than calling up every week and pushing your various systems.

Some surveillance systems are limited. Some don't try to get every possible case they can get. For example, in the immunization program, there are

surveillance systems that try to find out as many cases of varicella as possible, but in a very limited number of counties.

Data is collected in all different venues in surveillance systems or for surveillance purposes. I think classically what people have thought of as surveillance really are the notifiable disease reporting systems in the sense that these are infectious diseases that are required to be reported by law: measles, pertussis, HIV -- or at least right now AIDS cases, not just HIV.

Vital statistics systems.

As I mentioned before, there are sentinel surveillance activities.

Registries. I'll blur the line. Registries are in a sense a form of surveillance.

Health surveys are not surveillance per se, but they certainly serve surveillance purposes in the sense that one can look for trends over time.

There are also administrative data collection systems. I'll talk more about the Vaccine Safety Datalink Study in a while. Data sets that are collected for other purposes that are then turned to surveillance purposes.

I began my career at the Centers for Disease Control working on something called the Agent Orange project, and I'm pleased to see my original boss is in the

audience today, Dr. David Erickson. This was almost a 6-year effort, probably longer, to study the possible health effects of exposure to Agent Orange, and the active component there was thought to be dioxin in Vietnam veterans.

I just bring up this example because it was my first real good introduction to sort of a multi-layered approach. You had a basic question you were interested in answering, but there were many different ways to go about this in the sense that we looked at Vietnam veterans compared to other veterans, and we did a very layered approach. We looked at very large groups in terms of their survival. We looked at at a medium sized group in terms of doing interview, and then a much smaller group in terms of doing medical exams. Then for other types of outcomes, such as soft tissue sarcomas and other types of cancers, these groups were nowhere big enough to do those kind of studies so that they were actually multiple case-control studies that were performed using cancer registries, SEER sites, and other case finding mechanisms.

My next big experience was working in injury prevention. I spent most of my time working on a system called the Fatality Analysis Reporting System, which has been ongoing since 1975. What it does is it collects data on all fatal crashes involving motor vehicles, both on the

people who were in the vehicles, pedestrians, people who were on bicycles. It includes information on the persons who died and survived in those crashes. It has characteristics of the crash, such as the size of the vehicles that were involved.

Obviously, there are quite a few number of people that die each year in motor vehicle crashes. So, this is obviously a very large system. It has been going on for 25 years. It obviously it implies an enormous amount of infrastructure involved to collect all that data. So, in a sense it's a registry of everyone who has died in a motor vehicle crash. It's also a surveillance system in the sense you can look for trends over time and just the rates of those deaths.

We actually, when I was in the injury profession, used this data set to study the effects of seat belts and other individual and vehicle factors on the ability to survive a crash. I'm sure right now people look at those data quite eagerly to look at the effects of SUVs on survivability in a crash.

So, do we have a registry? Do we have a surveillance system? Do we have a mechanism to do epi studies? I think we have all three there.

In sexually transmitted diseases, I was involved with a number of surveillance systems.

Information comes to CDC via the National Electronic Telecommunication Surveillance System. This is basically the notifiable disease type setup. Three diseases that are very important to the STD group are syphilis, gonorrhea, and chlamydia.

But there's actually a very different way in which these surveillance data are viewed and treated by epidemiologists at CDC. The reporting for the syphilis and gonorrhea systems has been going on for a very long period of time, whereas for chlamydia reporting only started in the mid-1980s. When it started up, it was very incomplete and it is, by no means, complete even now.

So, for example, for syphilis reporting right now is felt to be fairly complete. It's a case-finding mechanism that is used for outbreak detection and outbreak control. It's used to allocate resources now in terms of trying to actually eliminate syphilis from the U.S.

Gonorrhea occurs at a much higher level, obviously. Again, it has had long-term reporting. It's incomplete but it's felt to be fairly stable at least within certain time periods so that one can go out and draw conclusions about are current intervention techniques working, are there changes in male to female ratios that might tell you something about the evolving epidemiology of the disease and so on.

Chlamydia is a very different kettle of fish in the sense that again surveillance for that disease only started in the mid-1980s. Over time more states have been reporting cases and there have been more reporting venues from within each state. So, if you look at a graphic of the number of reports of chlamydia over time, the graphic goes straight up, both for the country and within different states that report.

But if you look at other systems that provide test results, say, for example, from family planning clinics and other places that actually do treatment then of positive women, once those systems have been in place, you see the rates go straight down over time. So, obviously one would not use the chlamydia surveillance system to try to draw conclusions about trends and rates in the U.S. for chlamydia.

In the immunization program, there are a number of different types of surveillance activities. There is, of course, surveillance for vaccine preventable diseases themselves. There are national systems, again, for measles, rubella, tetanus, other diseases. There is national surveillance for varicella, but because of the extreme number of cases, it's certainly not felt to be complete. So, there are again sentinel sites in which there is an attempt to try to get a much more complete

reporting.

Certainly in these types of surveillance systems, just the number of cases themselves is a major point of the system. Just how many cases did we have last year, how many cases did we have this year is one of the most important pieces of information about those systems.

There are also other things that are collected. In these kind of situations, there is an important focus on vaccination status and the demographics of the cases. For example, people want to know, well, if there's an outbreak, is it due to a breakdown in vaccine efficacy? Has there been a series of bad batches of vaccine? Maybe there's waning immunity. After 10 years of being vaccinated, do we need to change our vaccination policy and have a two- or three-dose schedule? As an example, measles went from a one-dose schedule to a two-dose schedule.

It provides strategies for outbreak control. For example, the measles resurgence in the late 1980's/early 1990's, it was noted that a substantial number of cases were at ages below the recommended vaccination age in certain areas. So, the recommended vaccination age was dropped from 15 to 12 months in some large urban areas.

In the past, prior to the 1980s, there were a number of surveillance systems that looked at vaccine coverage. However, in the 1980s, money became scarce for

some of these activities and they were basically dropped. One thing that was found, as the measles outbreaks of 1989 to 1991 came about, people had no background information on national coverage rates for measles and certainly no estimation of what those coverage rates were at 1 year and 2 years.

So, in response to that and other fears about coverage in the 1990s, there are now several large surveys that do provide both national and very specific local information about coverage. But again, it took a long time for the surveys to get started. It wasn't a matter of 3 or 6 months before those systems were back in place.

The system that I have probably the most experience with is in vaccine safety. There have been a series of systems. From 1979 to 1990, the Centers for Disease Control ran a system called MSAEFI, which accepted adverse event reports that occurred after vaccines were given in the public sector, but not the private sector.

In 1990, there was an additional system, the Vaccine Adverse Event Reporting System, which is mostly run by FDA but also used quite extensively by CDC. That runs to the present and that accepts reports from all sources.

Now, this is a reporting system for exposed cases, so not only is it a numerator system, but it's also just a numerator system of those people who have also been

exposed to vaccines. But still a number of things can be done with this system, as we'll talk about in a minute.

The Institute of Medicine did two evaluations of the scientific knowledge concerning possible vaccine outcome associations and concluded that, for the most part, most of these suggested pairs that had come from anecdotal case reports, if you were categorizing them ala the pregnancy labeling type things, you would basically conclude that we just don't know. There's insufficient information to draw firm conclusions about most of these pairs, and that more telling, that there was insufficient available infrastructure in which vaccine safety surveillance and evaluation could actually take place. There had been several studies using Medicaid data, but they were sort of one off type epi studies and were very hard to keep going over time.

In response to these reports from the Institute of Medicine, CDC in collaboration with FDA and four large HMOs began a study now known as the Vaccine Safety Datalink. Data collection started in 1991 and is still ongoing. I think now probably close to 1 million children under 7 have been followed for some period of time in this cohort.

The initial focus of this study or surveillance system, depending upon your point of view, was to focus on

children less than 7 years of age and eventually it was expanded to adolescents and adults.

Now, there is an attempt to get complete vaccination information on these children. Actually a lot of the early years of the study were, in a sense, the HMOs building up their capacity to capture all this information and get it a timely fashion. In a sense they viewed that portion of the Datalink study as a vaccination registry. So, again, take your point view.

There also is medical outcome information. In all the sites, they have hospitalization information and emergency room information. Some of the sites also provide clinic based information.

And there is selected laboratory, pharmacy, and other covariate information, although not very extensive.

One of the points of view of the IOM was that VAERS and this cohort, this infrastructure should work in tandem, that there should be a signal generating mechanism and that the Vaccine Safety Datalink should be an opportunity then to evaluate those potential signals and see whether they actually held water in an identifiable cohort.

A couple years ago, I was involved in a study that followed this model. There was a potential signal in the VAERS data that identified a possible difference in the

rates of adverse events after two hepatitis B vaccines that were made by different manufacturers. These were fairly serious events, most of which required hospitalization.

So, we went to the Vaccine Safety Datalink data set and looked at this possibility. We had quite a few vaccinations from both these manufacturers across the four HMOs. So, the strength of this study was that had we had one HMO, possibly they would have had only manufacturer, whereas if we had four, there would have been much more likelihood that there were differences in this. We looked there. There was absolutely no difference by manufacturer in those outcomes in the Vaccine Safety Datalink, and there was not a problem with small numbers at all. Their confidence intervals were very tight and included one for the relative risk of the two vaccines.

It still isn't clear exactly why this signal was occurring in VAERS. The only sort of hint was that there appeared to a big difference in the usage of these vaccines in the private versus public sector and there may have been much more reporting of one of vaccines from one of those sectors. But that didn't seem to totally account for the difference in VAERS. So, it remains somewhat of a mystery, but it was very reassuring that there was no difference in the VSD cohort.

A more recent example is that of a Rotavirus

vaccine in intussusception. In mid-1998, a Rotavirus vaccine was licensed for use in the U.S. in infants. But in VAERS from September 1998 to July 1999, 15 cases of intussusception were reported to VAERS. This is a bowel obstruction in which one segment of your bowel becomes enfolded within another, and if it's not detected in time, it actually can be fatal.

Evaluation of this possible association was performed at one site in the Vaccine Safety Datalink. The results were similar to those from VAERS, but not totally conclusive.

One thing to note here is that it was not actually done on the routine administrative part of the data set because the usage here was, in a sense, too new for it to have made itself into the routine data set where there's at least usually a year lag time before it becomes available for analysis.

However, having the infrastructure in place and having the relationships in place, one can go and do special efforts in this kind of situation, which was done in this case, and get data on a more timely basis. But if there were no such study set up and no such relationships in place, it would obviously be much more difficult.

Currently a case-control study is being conducted by CDC to further elucidate this relationship.

However, in some sense, at least as far as the U.S. is concerned, it's somewhat of a moot point because currently at least the vaccine has been withdrawn from the market.

Currently I work on HIV/AIDS surveillance. HIV/AIDS surveillance data plays a very different role in the HIV program than surveillance does in the STD program in the sense that I think it's not too strong a statement to say that the HIV and AIDS surveillance data is really the core generator of what other questions people want to look at. It's sort of the bedrock thing that people go back to in terms of we've been doing this intervention for a long time. Is it making a difference?

The reason that it plays the different role in HIV/AIDS than it does in STDs is really, I think, for the most part, in its completeness, at least on the AIDS side, obviously not so much on the HIV side. But given its near completeness on the AIDS side, one can make firm conclusions, for example, just on pure case numbers in some instances.

But there also is a very layered approach to HIV surveillance activities in the sense that the main system, the HIV/AIDS reporting system, all 65 programs report AIDS cases to CDC. Currently about half of those programs report HIV, although that's increasing every year. Eventually we hope that that is all 65 programs.

In that system, some data is sought more than others. I think probably the data that's sought most assiduously in that system is the background information on the risk factors, in other words, the probable mode of transmission. So, again here we have a system that's meant to incorporate everybody, and while it tries to get a fair amount of information, it really is a two- or a four-page questionnaire.

But there are additional systems in restricted sites. Some of these are ongoing, so they are viewed as surveillance systems in their own right, for example, the Adult Spectrum of Disease and the Pediatric Spectrum of Disease which both started in the early to mid-1990s and originally were meant to look at natural history disease, especially opportunistic illnesses in relation to HIV disease. But as treatments have become more widespread, they also provide an opportunity to look at patterns of care, usage of drugs, combinations of drugs.

However, they weren't always set up to be completely representative of either the U.S. or even areas they were in. So, there are some additional studies starting up. For example, HIV Care Sampling is meant to be a more population based estimate of what type of care is being given to people with HIV. Now, these are ongoing systems that do have their own ongoing infrastructure.

There are also more short-term goals in the sense that there are some studies that look at pediatric transmission. There have been studies on enhanced pediatric surveillance, and another study, AIDs progression, looking at reasons why now in an era of very viable therapy, what are the characteristics of those people that either go on to get AIDS or go on to die with AIDS. But these are viewed as more short-term efforts. They are conducted from surveillance programs, but they are done in maybe 8 or 10 sites and they may be done for a year or two, whereas these may be done at 8 or 10 sites, but they're done for 10, 15, 20 years. Again, these are done everywhere.

There obviously were a variety of issues that this workshop was built around, pregnancy labeling guidelines, guidelines for setting up pregnancy-drug registries, and even a proposal to consider a workshop on a centralized pregnancy-drug registry.

To me it was very interesting to read the guidelines for setting up the registries. You read these things, and boy, this sounds like a great idea, all these different proposals the person is making sound great. Then it's kind of like you've listened to one political candidate and now you turn and listen to the other. You read the problems that are raised by the various drug

companies, and you go, yeah, what about that.

But there were some very good points made there, and I think I've tried touch on some of those in a way in some of the things I've said. This is not meant to be exhaustive but I think that this is representative of what those concerns were.

For example, should we limit registries to those drugs that are already under suspicion or should we try to get at all drugs or at least some larger class of drugs?

Are we trying to evaluate only new drugs, or what are the criteria that we would want to look at older, established drugs? Or do we want to maintain ongoing surveillance of older, established drugs?

From the point of view of maybe a new type of person who's going to be taking them or, for example, to make a vaccine analogy, can there be bad batches of drug?

There was a lot of concern that requests for background information about drug usage by pregnant women was very hard to come by and maybe in some sense that's one thing the pregnancy registry was going to find out rather than needing to have it before you could start doing it.

In many cases the range of suggested outcomes to be followed in the context of one registry was considered to be too broad, requiring multiple sources of