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DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Volume II

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8:05 a.m.

Holiday Inn
8777 Georgia Avenue
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PARTICIPANTS

Peter Gross, M.D., Chair
Shalini Jain, PA-C, Executive Secretary

MEMBERS

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Ruth S. Day, Ph.D.
Curt D. Furberg, M.D., Ph.D.
Jacqueline S. Gardner, Ph.D., MPH
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Louis A. Morris, Ph.D.
Richard Platt, M.D., M.Sc.
Robyn S. Shapiro, J.D.
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Elizabeth Andrews, MPH, Ph.D.
Sean Hennessy, Pharm.D, Ph.D.
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Mark Avigan, M.D., C.M.
Gerald DalPan, M.D., MHS
Carol Holquist, R.Ph.
Paul Seligman, M.D., MPH
Anne Trontell, M.D., MPH

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. GROSS: This is the second day of our meeting exploring issues related to FDA's Risk Assessment Program for marketed drugs.

We will begin today, because there are some new people in the audience, by going around and introducing ourselves and saying what our area of interest is.

Paul, do you want to begin?

DR. SELIGMAN: Good morning. I would be delighted. My name is Paul Seligman. I am the Director of the Office of Pharmacoepidemiology and Statistical Science in CDER at the FDA.

DR. TRONTELL: I am Anne Trontell. I am the Deputy Director of the Office of Drug Safety in FDA Center for Drugs.

DR. AVIGAN: Good morning. I am Mark Avigan. I am the Director of the Drug Risk Evaluation Division in the same office.

DR. DALPAN: Good morning. I am Gerald DalPan. I am the Director of the Division of

Surveillance, Research and Communication Support in CDER's Office of Drug Safety.

DR. GARDNER: I am Jacqueline Gardner, University of Washington in Seattle, and Professor of Pharmacy.

DR. STEMHAGEN: I am Annette Stemhagen. I am an epidemiologist at Covance and I am the Industry Representative on this committee.

DR. FURBERG: I am Curt Furberg. I am from Wake Forest University. I am Professor of Public Health Sciences.

MS. SHAPIRO: I am Robyn Shapiro from Medical College of Wisconsin, Ursula Von der Ruhr Professor of Bioethics and Director of the Center For Study of Bioethics.

DR. MORRIS: Lou Morris, President, Lou Morris & Associates.

DR. HENNESSY: I am Sean Hennessy. I work at the University of Pennsylvania doing drug safety research.

DR. GROSS: I am Peter Gross. My main interest is in quality improvement in health care

and developing new systems of care I am Chairman of the Department of Medicine at Hackensack University Medical Center and Professor of Medicine at New Jersey Medical School.

MS. JAIN: Shalini Jain, Health Science Administrator, and Executive Secretary for this committee.

DR. CRAWFORD: Good morning. Stephanie Crawford, Associate Professor, University of Illinois at Chicago, College of Pharmacy. My area is evaluation of safe medication systems.

DR. MITCHELL: Allen Mitchell, Director of the Epidemiology Center at Boston University. My interests are pharmacoepidemiology and drug safety.

DR. PLATT: I am Richard Platt. I am Chairman of the Department of Ambulatory Care and Prevention at Harvard Medical School and Harvard Public Health Care.

DR. ANDREWS: Elizabeth Andrews, Vice President for Pharmacoepidemiology and Risk Management, Research Triangle Institute.

DR. DAY: Ruth Day, Duke University. I do

research on comprehension of drug information by physicians, consumers, and others.

MR. LEVIN: Arthur Levin, Center for Medical Consumers in New York. I am the Consumer Representative.

Conflict of Interest Statement

MS. JAIN: I am now going to read the Conflict of Interest Statements. There are two, so please bear with me.

I also want to just make a quick announcement that we are going to have a slight modification to the agenda. Dr. Beitz's presentation is going to be flip-flopped with Dr. Graham's, so in your programs, at 9:10 a.m., you will be hearing from Dr. Graham, and at 10:10 a.m., assuming we are running on time, you will be hearing from Dr. Beitz.

The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda of the

advantages and disadvantages of the current system for safety signal detection and proposals for short- and long-term ways to improve the current system, and all financial interests reported by the committee participants, the agency has determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), Dr. Richard Platt has been granted a waiver which permits him to participate in today's discussions. A copy of this waiver statement may be obtained by submitting a written statement to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

The Food and Drug Administration has prepared general matter waivers for the following special government employees: Drs. Louis Morris, Peter Gross, Elizabeth Andrews, Ruth Day, Sean Hennessy, and Allen Mitchell, who are participating

in today's meeting of the Drug Safety and Risk Management Advisory Committee, on the types of population-based studies that can be used to assess safety, for example, clinical trials for new indications, registries, Phase IV postmarketing studies and epidemiological studies. This meeting is being held by the Center for Drug Evaluation and Research.

Unlike issues before a committee in which a particular product is discussed, issues of broad applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions. The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they apply to each member.

The FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the Committee, the potential conflicts are mitigated.

With respect to FDA's invited Industry Representative, we would like to disclose that Dr. Annette Stemhagen is participating in this meeting

as a Non-Voting Industry Representative acting on behalf of regular industry. Dr. Stemhagen's role in this committee is to represent industry interests in general, and not any one particular company. Dr. Stemhagen is employed by Covance, Incorporated.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

Thank you.

DR. GROSS: We will begin with opening remarks from Dr. Paul Seligman.

Opening Remarks

DR. SELIGMAN: Good morning. It is a pleasure to welcome you all back this morning to day two of our Drug Safety and Risk Management Advisory Committee meeting. I apologize for my softness of my voice, a little bit of hoarseness,

but I will try to use the microphone to its maximum.

Yesterday, we had a very stimulating discussion about a number of surveillance methods including the Adverse Event Reporting System, the use of drug utilization data, and other surveillance approaches to assessing drug risks in the postmarketing environment.

Today, we are going to shift and focus on other areas important to this assessment including population-based studies, the use of registries, and the use of postmarketing studies from both an industry, as well as FDA review division perspective.

We also yesterday heard I think a number of very interesting and provocative presentations

during the open public session, and we will have again today an opportunity for additional presentations during the open public hearing portion of this morning's agenda.

The questions we are going to be posing to the committee today include under what circumstances should epidemiologic studies and other approaches, such as ongoing clinical trials in the postmarketing environment, be used, and under what circumstances are they best suited to detect the risk of drugs in the postmarketing environment.

Are there particular safety problems or safety issues that are best suited for the conduct of population-based studies? What are the criteria that the FDA should use to prioritize its drug safety signals for quantification by using population-based studies, and how should FDA expand its access to data needed to conduct such studies?

In many ways, we have answered or at least begun to approach some of these questions yesterday in talking about surveillance techniques and

hopefully, today, we can further expand and refine that discussion.

Finally, at the end of the day, we are going to ask the committee to provide us essentially a wrap-up and ask them, given all of the methods discussed both yesterday and today in terms of conduct of surveillance, as well as observational or population-based studies, where we should focus our efforts in the short term over the next 6 to 18 months, as well as in to the long term over the next, say, 18 months to 5 years, in terms of devoting our resources and efforts and improving our assessment of the safety of drugs in the postmarketing environment.

Again, we are looking forward to the discussion today. My role yesterday, as well as my role today, is to get us right back on time with the agenda, so my remarks are brief.

With that, I would like to turn the committee back over to you, Mr. Chairman, for the conduct of today's discussion.

Thank you, all.

DR. GROSS: Thank you, Paul.

The next speaker will be Dr. Gerald DalPan, who is Director of the Division of

Surveillance, Research, and Communication Support in the Office of Drug Safety.

He will discuss an Overview of Drug Safety Challenges.

Overview of Drug Safety Challenges

DR. DALPAN: Good morning. My name is Gerald DalPan. I am the Director of the Division of Surveillance, Research, and Communication Support in FDA's Office of Drug Safety.

What I would like to do today is just really set the frame for the subsequent talks you will hear after mine, as well as for the discussion that will follow later today.

Yesterday, we heard about the passive spontaneous surveillance system that FDA currently uses to identify new adverse drug events. My colleagues spoke about, and the Committee spoke about, the strengths and limitations of the systems and how it is currently used in FDA's postmarketing

drug surveillance efforts.

We also heard about some new developments in active surveillance systems and how these systems may improve identification of adverse drug events in certain settings.

Finally, we heard about drug utilization databases and how these databases can play a sometimes important role in framing the context of the newly identified adverse event.

Today's talks and the discussion that follows will be focused on population-based studies, clinical trials, epidemiologic studies, such as case-controlled studies and cohort studies, and registries. We will have talks by FDA representatives on this, and we will also hear from an industry representative on these topics.

[Slide.]

In my talk, I would like to set the stage for today's discussion by describing for you the many types of challenges that we face when identifying a new adverse drug reaction.

I will try to present several situations

in which a spontaneous report of a new potential adverse drug event could arise and I will review the challenges in the interpretation of these spontaneous reports in different settings.

With regard to the investigation of risk, I will also briefly review some of the possible methodological approaches using population-based studies that can be used to further characterize these risks.

Then, I will discuss some ways that understanding the context of drug use can inform our understanding of the population prevalence of certain adverse events. By design, I am only going to talk about the highlights of these issues. You will hear more about them later this morning.

Rather, the talk is really just to set the stage for further discussions today.

[Slide.]

Well, identifying new adverse events is a fundamental goal of our postmarketing drug safety programs, because when any drug is newly brought to market, its safety profile, though well

characterized in the premarketing studies, is incomplete, and that's for a few reasons.

The main reasons are that the clinical development program can't detect all events especially rare events, and second, when a drug is rolled out into the market, the use of that drug in actual clinical practice doesn't always mimic what happened in the more controlled setting of a clinical trial.

So, these are the two big reasons that events can occur in the postmarketing setting that weren't identified in the premarketing setting.

A program to identify new adverse drug events must then be able to account for these many different types of risks, such as those that are inherent in drug and those that emerge really once actual practice with that drug is gained.

In addition, a program to identify new adverse drug reactions must be able to account for many potential confounding factors. Such factors may at a first glance obscure the association of a drug with an event and only after careful study

will the true association then emerge.

Finally, a drug safety program must be able to account for the time course of adverse drug reactions. For example, some risks for adverse events may occur only if the drug is used for a long period of time. This is something that is important to understand.

[Slide.]

When a drug is first brought to market, there is really a considerable body of pre-clinical and clinical safety information. This information comes from the pre-clinical studies, the clinical pharmacology studies, the controlled safety data, that is, clinical safety data from controlled clinical trials, and clinical safety data from open-label studies. These are often long-term extension studies which often provide a lot of long-term safety data.

This forms the premarketing safety database.

[Slide.]

So, when a drug is brought to market here,

we have this premarketing safety database as sort of an anchor. This is what prescribers can rely on. The drug has been introduced into the market and then there is this long postmarketing period where our pharmacovigilance activities take place, and new adverse events can happen.

[Slide.]

In these slides, a red oval here will represent a new, previously unrecognized potential adverse drug event, and a series of red ovals will represent a set of similar events. Then, the challenge for a postmarketing safety program is really to make sense of them, what do they mean, how do we interpret them, and what is it about these events that allows us to make an association or that hinders us from making an association when an association may really exist.

[Slide.]

So let's look at some different examples, some different settings. Here we have an example of a few adverse events occurring shortly after the introduction to market of the drug.

In my talk, I will use three or four red ovals to indicate a small number of events, and 10 or 15 red ovals to indicate a large number, and I

want to stress that this is arbitrary, these numbers are arbitrary rather and are simply used in the context of the diagrams I am using schematically today.

So, in some cases, the identified event is rare, not only in the general population, but it is also rare in the population of persons with the disease for which the drug is taken. Examples of these rare, but serious adverse events would be aplastic anemia, drug-induced lived injury, and we heard yesterday from my colleagues about some serious skin reactions, such as Stevens-Johnson syndrome.

These are the kind of events that the spontaneous passive surveillance system is designed to identify, and I think we heard yesterday does a pretty good job at. However, things aren't always this simple or clear-cut.

[Slide.]

In this example, we have a large number, a large set of a particular adverse event that occurs once a drug has been brought to market, and for the sake of this example, we will call this event a myocardial infarction.

So, if this drug is being used in a large

group of older persons who would have a reasonable background rate of myocardial infarction, we have the situation here where the adverse event we are seeing in spontaneous reports is also common in the population, and the challenge for a drug safety program here is to determine if the observed cases of myocardial infarction represent a true risk of the drug or if they are fully explained by the background rate of myocardial infarction in the population using the drug.

[Slide.]

Another example here, we have the same large number of adverse events. For the sake of argument, we will say this is a myocardial infarction again. Here, instead of being simply used in people who may otherwise have myocardial

infarction, let's say this drug is used to treat ischemic heart disease.

Here, the challenge for the drug safety program is to see if these observed events represent a risk of the drug or if they are simply a manifestation of the disease being treated. Dr. Weaver used a similar example yesterday with asthma exacerbations in a drug used to treat asthma.

[Slide.]

So, in both of these cases, the real issue is how do we separate a potential signal from the background?

[Slide.]

Other challenges can also exist. For example, there may be a long latency between taking the drug and developing an adverse event. There was some discussion of this yesterday.

Here, not only is there a long latency between when an individual person takes the drug and the development of an event, but because of that long latency in individual persons, there will be a latency between when the drug is introduced to

market and when these adverse events occur.

[Slide.]

So, up to this point, we have really assumed that adverse drug reactions are due solely to the intrinsic properties of the drug in susceptible recipients, and we haven't assumed that external factors can also influence the development of an adverse drug event, but external factors can influence the development of adverse events, and those are important to consider in a postmarketing drug safety surveillance program, as well.

I have a number of adverse events here and I have indicated external factors by these little green diamonds on top, and example of these external factors or effect modifiers would be drug-drug interactions, drug-disease interactions, drug-herbal interactions, and drug-food interactions.

Again, these are the kinds of things that can occur once a drug is introduced to market that may not have been identified in the premarketing safety database, and yet each of these

interactions, if they result in a serious adverse event, is important to detect.

[Slide.]

The external factor leading to an adverse event doesn't necessarily have to be another substance like a drug, food, or herb. The external factor can be a condition of how the drug is used. An example would be a medication error. For example, people could give the wrong dose, or they could give the drug to somebody with a known contraindication to that drug. Here, we have indicated these external factors as green triangles.

It is important that a surveillance system be able to identify the medication error. This is an example where good reports, as Commander Holquist mentioned yesterday, count. Somebody received a drug when they had a known contraindication to it, but the report doesn't say that they had the contraindication to it, it would be hard to know that that was a medication error in that particular case.

[Slide.]

So, how do we look at these events? With a passive spontaneous adverse event reporting

system, the individual case report is really the cornerstone of the system, and Dr. Weaver spoke extensively about that yesterday. So, the evaluation of the individual reports is really the starting place for the evaluation of a potential new adverse drug event.

So, we can go back to the case of these rare but serious adverse events. These were the things like aplastic anemia, drug-induced liver injury, and here we can have intensive case evaluation, which is really, as I said, the cornerstone of the analysis of these adverse events.

If we have complete case reports with adequate follow-up, these can shed considerable light, not only on each of the reported events themselves, but more importantly, on the set of events that we have observed. In some cases, the premarketing safety database may also inform our

thinking about these although if they are truly new adverse events, then, we wouldn't have precedence in the premarketing database.

So, if the observed event, as in this case, is not expected in the population being treated, and if there is no potential external effect modifier that could confound the association of the drug with the event, then, intensive case evaluation here may be sufficient to establish the association between the drug and the event, but as we heard yesterday, things aren't always this simple.

[Slide.]

So, here we have our cases of myocardial infarction here that are either common in the population in some cases or manifestations of the underlying disease in other cases.

Here, intensive case evaluation is unlikely to establish a pattern of events that would reliably distinguish a drug-associated event from a background rate of event in the patient population.

Review of the premarketing safety database is also unlikely to shed a lot of light on this if these events, in fact, were never previously

observed. So, it is very hard to establish a drug-related risk in this situation and it is even harder, if not impossible, to actually quantify that risk.

So, for these types of situations, more extensive analysis is needed. In these situations, it is often necessary to go to other databases or to other sources of data rather. In some cases, sources of data that already exist, in other cases, data must be generated to answer the question at hand.

So, now I would like to review very briefly the basic structure of the types of studies that can shed light on some of these not so clear-cut safety challenges. I won't go into any detail in any of them. You will hear from the other speakers this morning who will have talks dedicated to these topics. Rather, I will give a brief overview of the basic principles of these

methods.

[Slide.]

The clinical trial is probably the best known method for determining if a drug has a particular effect. Usually, clinical trials are designed specifically to determine an efficacy effect, but the principles of clinical trial design can also be used to determine if a particular safety issue exists.

I won't dwell on the design of a clinical trial. Dr. Beitz will speak in greater detail about design of clinical trial and challenges this morning. Let me go over the basic outline.

In brief, persons who meet protocol defined entry criteria are assigned, usually randomly, to one of two or more treatments. These subjects are then followed for a defined follow-up period at regularly scheduled interviews with a structured evaluation at each of those intervals.

Outcome information, including information on safety and adverse events, is collected in a systematic and standardized fashion, and if there

is a particular concern about identifying a particular safety problem, the outcome measures in the protocol can be tailored to capture the events of interest as accurately and in as much detail as possible.

There are many variations on this design. For instance, you can have three or more treatment groups, you can have a run-in period to individualize dosing. There can be washout periods to remove the effects of previously administered treatments, and there can be crossover between treatments, but the basic feature of the clinical trials, that is, the protocol-defined treatment allocation, treatment administration, and standardized follow-up is really common to all clinical trials.

So, how can clinical trials help answer questions about drug safety?

[Slide.]

Well, we can go back to these large number of adverse events that are just sitting here, where we don't know the relationship between treatment

and non-treatment, and when we do a clinical trial, we can see how they occur in the group not treated with the drug of interest and in the group treated with the drug of interest.

[Slide.]

We see here that we have some additional adverse events in the treated group. As before, the number of red ovals, three in this example, isn't meant to be a literal interpretation that these three events represent excess risk. Rather, this is a schematic view of how adverse event data can be ascertained from clinical trials.

In addition, circling these three particular events doesn't mean that these three events were due to the drug and the others weren't, rather, it just means that this is an excess risk noted in this clinical trial, and this risk can be quantified in a risk ratio.

So, clinical trials can be useful in many situations for understanding adverse events associated with drugs especially those where the adverse event is either a manifestation of the

disease being treated or is otherwise common in the general population.

We are going to ask you later today to discuss the role of clinical trials, including postmarketing clinical trials, in understanding adverse events that develop in the postmarketing setting.

[Slide.]

Epidemiological studies can also play a role in understanding potential new adverse drug events. For example, a case-controlled study can be used to measure the association between an adverse event and prior exposure of the drug. Again, I will just mention the brief features of a case-control study.

In this design, persons with the event of interest are identified. Here they are, four persons with the red ovals, and controls are also identified. These are people who don't have the outcome of interest. These are the group with the turquoise ovals.

Several mechanisms can be used to identify

these persons. They can be identified in registries, they can be identified in medical records and medical claims data. They can be identified in cohort studies, or they can be recruited and persons without the event of interest, the turquoise ovals here, can be identified in a similar fashion.

The next step then is to ascertain exposure - do they take or did they ever take, depending on the particular question of interest, the treatment of interest. Then, once we have these two pieces of information, who has the outcome and who doesn't, who took the drug and who didn't, we can try to make an association between the drug and the event.

The standard schematic for this is the familiar 2 by 2 table where we divide the cases and controls into those who are treated and those who are not treated. This is the simplest way of doing it although more complex statistical methods are often employed. So, a measure of the association, the odds ratio can then be obtained.

There can be many variations on this design, I won't go into it in detail. Dr. Graham will later discuss some of the challenges in

implementing this design later this morning. Nonetheless, the case-control study can be used to measure the association of a drug with a particular event of interest. This method may be particularly well suited to understanding the association of an event to a drug when the event is too rare to be detected in clinical trials, but not so rare that it wouldn't be detected in the methods you use to ascertain cases.

[Slide.]

Another type of study is the cohort study. In this design, persons are followed from an established start period, from a specific time point, and they are followed over time here. These are what the white lines represent, and they are followed both for usage of the drug, that is what these green lines mean, these green lines mean that people are taking the drug, and note that not everybody takes the drug in this cohort study, and

they are also followed for development of the event of interest.

Again, in some cases, the event of interest occurs in persons on the drug, while on the drug. It can occur in persons who have taken the drug, but while they are no longer on it. It can occur in persons who have never taken the drug.

The statistical method used to evaluate such studies are complex. Again, Dr. Graham will talk more about these kinds of studies later this morning, and I won't dwell on them here, just suffice as to say that a measure of risk, a quantitative measure of risk, such as a relative risk or a hazard ratio, can be obtained.

[Slide.]

Another method for studying potential adverse drug events relies on the use of registries, and the term "registry" can have many meanings in this setting. Our guidance document on good pharmacovigilance practices uses a definition from the National Committee on Vital and Health Statistics that defines a registry as, in

quotations, "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention for either a particular disease, a condition, for example, a risk factor that predisposes them to the occurrence of a health-related event, or prior exposure to substances or circumstances known or suspected to cause adverse health effects."

It is a very broad definition and it reflects the fact that registries can be used in a variety of public health settings. Here, we can take a look to see how registries could be used to shed light on adverse events.

So, a common type of registry is a disease registry, so the registry here is this big oval, and the persons with the disease of interest are indicated in yellow inside, and this type of registry can be used in a variety of ways.

It can look backwards in case-control studies, as I mentioned before, these persons can form the cases in a case-control study, and if the

disease of interest is a potential drug-related adverse event, we could use these persons to study the relationship of the drug to the event.

Second, for public health purposes, the magnitude of the disease in the population can be estimated, and finally, disease registries can be used to study the natural history or survival of the disease.

So, with regard to drug safety, it is this first use that may be more informative for us.

[Slide.]

We can also study persons with an exposure of interest, and in our case, the exposure of interest was did you take this drug, so these are people who have taken the drug. Again, we can look backwards, why are people taking this drug, how many people are taking this drug although we have drug use databases that answer that question for us.

Perhaps most importantly for drug safety, we can use registries to look at what the outcome of exposure is. I won't dwell on this. Dr. Uhl

will talk about the use of registries later this morning and she will focus on pregnancy outcome registries.

[Slide.]

Just let me shift my attention now to how we can use drug use information and other information to really further refine our understanding of adverse events by understanding their context.

The first thing I would like to talk about is understanding the time course of adverse events relative to initial exposure to the drug and to the duration of exposure. In some cases, the risk of an adverse event from the drug is independent of the duration of exposure.

So, over here we have risk on the y axis, duration of exposure on the x axis, and the orange line indicates that the risk is the same across a wide range of durations of exposure. In other cases, the risk of the adverse event is highest early in exposure to the drug and then it levels off, often to low levels, and this is what this

green line indicates.

Finally, the risk can occur only after prolonged exposure to the drug as indicated in the red graph here, and if there is concern that this is the case, it is important that this period of exposure be studied.

Now, if we understand the risk of adverse events as they relate to duration of exposure, we can then better understand the public health impact of risk if we know how long people actually take the drug for once it's on the market, and this is where population-based drug utilization databases can help.

[Slide.]

So, here, we are going to plot duration of exposure and the number of persons taking the drug. This is the kind of information we could get from drug utilization databases.

Here, we see that equal numbers of persons take the drug for different lengths of exposures, the same number of persons take it for a long time as take it for a short amount of time.

[Slide.]

In this slide here, we see that use is really concentrated on short-term exposure with

relative little long-term exposure.

[Slide.]

Conversely, here, we see relatively little short-term exposure, but lots of long-term exposure.

[Slide.]

So, how can we use this information? Well, if there is a particular adverse event of interest, and we know that the risk of that adverse event occurs primarily after a long exposure, we can use our drug utilization data on exposure to see what the population burden of that event is, is there really can be a risk based on what we know about the risk profile and based on how the drug is actually used.

So, in this case, if our population drug databases tells us that the drug is really used for a short period of time, it is unlikely that adverse events of this type will emerge.

However, if we have this kind of usage pattern here, with a substantial long-term use, then, there really are potential for many adverse events. So, this is how the context of use of the drug can inform our knowledge of risk for what the public health burden of an adverse event might be.

[Slide.]

Finally, another way we can use drug use databases is to look at the potential for adverse drug-drug interactions or really adverse events related to adverse drug-drug interactions.

So, let's say we have two drugs. We will call them A and B, and they are known to have a drug-drug interaction that can produce a clinically serious, serious adverse event. We know that already. Our studies have told us that.

We want to see how is this drug being used in the population, because we know that the prevalence of concomitant use will determine the prevalence of the adverse event related to such concomitant use.

So, we can use drug utilization databases

to tell us there is no concomitant use, so we wouldn't have much risk. There is a low level of concomitant use, so we would have some risk, or there is a high level of concomitant use, so we would have some prevalence, I should say, not risk, but there would be some prevalence of this adverse event out there, and population databases can help us understand the risk in the population based on what we know about the clinical pharmacology of a drug and how the drug is used in the population.

[Slide.]

So, in summary, then, I have tried to review some of the challenges that a postmarketing drug safety program must address. I have tried to show that there are multifaceted challenges to such a program, that the identification of an adverse event in a postmarketing setting, or the investigation rather has to be focused on what the nature of the problem is, because the problem isn't always the same.

I have tried to show that there are many ways to explore risk - intensive case evaluation,

clinical trials, epidemiologic studies, registries, and you will hear more about those later this morning, and we will ask you to address the role of those later today.

Finally, I have tried to show how understanding the context of how drugs are actually used can be important.

So, thank you, and I will turn it back over to Dr. Gross.

DR. GROSS: Thank you very much. That was very instructive.

The next speaker is Dr. Kathleen Uhl of the Pregnancy and Lactation Team of the Office of Drug Safety, who will talk about Pregnancy Exposure Registries.

Pregnancy Exposure Registries

DR. UHL: Good morning. My name is Kathleen Uhl. I am with the Pregnancy and Lactation Team in the Office of New Drugs at CDER.

Dr. DalPan introduced the concept of registries as one type of population-based studies to ascertain risk from drug exposure. Well, my

presentation will focus on only one specific type of registry. It will focus on pregnancy exposure registries.

These type of registries are one tool that can be used to evaluate fetal risk from exposure to pharmaceutical products during pregnancy.

[Slide.]

What I plan to do this morning is to give you some background to put the context of drug use in pregnancy or to put that issue into context as we talk about this.

I will provide a definition for pregnancy exposures basically as defined in FDA guidance documents.

Next, I will provide some types of pregnancy exposure registries that are out there and some information on when registries might be considered and why, what products might be good candidates.

I will discuss some of the benefits of these registries, as well as the limitations, and end my presentation with the challenges of these

type of studies.

[Slide.]

Just to put the issue of drug use in pregnancy into some context, it is important to understand the amount of pregnancies that occur in our country, as well as some of the drug use during pregnancies. So, in the U.S., there are 60 million women of childbearing age, and each year, 10 percent of those women become pregnant. So, that equates to approximately 6 million pregnancies and over 4 million live births.

[Slide.]

Pregnant women need medications. They enter pregnancy with medical problems that need medical treatment, for example, seizure disorder, asthma. Pregnant women also develop new medical problems that require therapy, for example, infections quite common in pregnancy, pregnancy-induced hypertension just based on diabetes.

We know that pregnant women use medications. There are survey data that have been

conducted in the U.S., as well as in Europe, that show that pregnant women use approximately 5 medications per pregnancy, and that excludes prenatal vitamins, as well as iron, and the number of drugs increases with older women.

Because in the U.S., 50 percent of the pregnancies are unplanned, that creates a situation where inadvertent exposures to drugs during pregnancy would be quite common, for example, a woman that is taking a medication and doesn't realize that she is pregnant yet.

[Slide.]

So, what do we know about drug effects in pregnancy and how can we use information to guide treatment in pregnancy or counsel pregnant women about exposures?

Well, the problem is that at approval, there are no data on drug effects during human pregnancy. Although the issue was brought up about clinical trial data, there are no clinical trial data for pregnancy unless, of course, the drug is being developed for a specific indication in

pregnancy.

This is largely because pregnant women are excluded from clinical trials, so the risk information for human pregnancy is derived exclusively from animal data.

So, what we have to do then is depend on postmarketing surveillance to assess human fetal safety, and this has historically relied upon spontaneous reports. You heard yesterday some of the limitations of spontaneous reports.

The primary concern, though, for drug exposure during pregnancy is typically teratogenesis. There are certainly other issues, but I will focus this on teratogenesis, which is the issue of birth defects.

[Slide.]

Before I continue, I think it is important to look at drug effects in pregnancy with a little different focus than we have been talking about postmarketing safety. It's a little bit of a paradigm shift because what has been discussed so far is an adverse event in the patient who is

taking the drug.

Here, what we have is that we are not looking at the safety in the patient who is being treated, but rather we are looking at the impact of that on the developing fetus.

Also, traditionally, with postmarketing safety, we are looking for a signal. In the area of drug exposure during pregnancy, it is important, probably even more important to be able to say there is no signal and there is no increased risk from drug exposure during pregnancy.

[Slide.]

So, one method to collect information on drug exposures during pregnancy and associated fetal risk is through a pregnancy exposure registry. The Agency has published guidance for these type of studies, and this guidance was published in its final form in 2002.

[Slide.]

The guidance document is really a "how to" document. It is a document that is useful when someone is trying to plan one of these studies. It

discusses protocol development, as well as some of the design considerations.

[Slide.]

What this guidance does, though, is it defines a pregnancy exposure registry, and the definition of a pregnancy exposure registry per this guidance document is, "A prospective observational study that actively collects information on medical product exposures during pregnancy and associated pregnancy outcomes."

So, enrollment in this study is based on drug exposure that occurs before the outcome of the pregnancy is known. Then, the birth defect rate is the exposed group is compared to either the background rate for birth defects or to a comparison group or groups.

But what I draw your attention to is that it is defined as a study.

[Slide.]

Now, the whole nomenclature of registry is very problematic, and I think as the Committee discusses registries this afternoon, it is

important to know what are you talking about, what do you mean by a "registry."

A colleague of mine presented at a meeting a couple of years ago, and the meeting was specific about registries, and she was presenting on pregnancy exposure registry, and the keynote speaker at that meeting said a registry is not a study.

So, in a more traditional sense, what is a registry? It is a list of patients. The collection of that patient list is not protocol driven, the data collection is not protocol driven, and the data analysis is not protocol driven.

So, registries can be extremely broad in scope, there can be tremendous variability in the amount of the data and the type of data that are collected. Registries focus oftentimes on patient satisfaction, and the data from registries are used for marketing purposes.

[Slide.]

The Office of Women's Health at FDA has a registry website. This website is geared

specifically for consumers. It provides information about what is a pregnancy registry, and it also has a list of registries that patients can find and what registries are actively enrolling pregnant women.

[Slide.]

There are multiple different types of registries, and I guess registries could be looked at or categorized in multiple ways, but this is just to give you some idea of the diversity of registries.

In addition, there will be specific registries mentioned, specific drug names mentioned. These are really just for illustration purpose. It is not really to single out any specific drug or any specific company.

But registries, by and large, are voluntary. They are voluntary on the part of the patient, they are voluntary on the physician or healthcare practitioner, and they can be voluntary on the part of the manufacturer.

In addition, registries can be mandatory.

Actually, we know that that means required, and that could be as part of a Phase IV commitment.

[Slide.]

There can be country-specific registries like the UK Anti-Epileptic Drug Registry, and registries can be international. They can enroll patients from multiple different countries, and that is quite common.

[Slide.]

Registries can be disease-specific, as Dr. DalPan mentioned, but registries, as far as pregnancy registries are concerned, here are a few examples. There is a rheumatoid arthritis pregnancy registry, which is run by the Organization of Teratogen Information Services or OTIS.

There is a seizure disorder registry called the Anti-Epileptic Drug Pregnancy Registry run by Lou Holmes, and there is also a registry under development very close to being launched for allergy and asthma. This is a unique joint product of OTIS and the American Association of Asthma,

Allergy, and Immunology.

What is unique about this registry, though, is that it pairs a traditional registry design with case-control studies, and then there are drug-specific registries, and I will provide some examples of that.

[Slide.]

Registries could be a single drug, a single company registry, like the Lamotrigine Registry that GlaxoSmithKline has.

They could be a single drug, multiple-company registry, such as the Ribavirin Pregnancy Registry. This registry is interesting in the fact that it's the first of a type, a prototype whereby the companies are the innovators for Ribavirin, as well as several generic manufacturers.

Registries could be multiple drugs within a single company, and the Merck Pregnancy Registry Program is an example of this. Many companies think that they are doing this, but in essence what they are doing is typical postmarketing

surveillance, the collection of pregnancy exposure data and outcome is not protocol driven. It is what you have heard about in the last day.

There are also multiple drugs, multiple company registries, like the Antiretroviral Pregnancy Registry.

[Slide.]

Registries can be designed and run by the manufacturer. An example is the Avonex Registry which is run by Biogen.

Registries can be coordinated and run by Contract Research Organizations, and I have three examples here that are Inveresk Company Registries. There registries include the Ribavirin Registry, the Lamotrigine, and the Anti-Retroviral Pregnancy Registry. There are certainly other CROs that do this, and also registries can be coordinated and run by scientific organizations or academic institutions.

The OTIS group, that I mentioned earlier, and the Rheumatoid Arthritis Study that they have. The Motherisk Program out of Toronto is also part

of the OTIS group, and they have an Antipsychotic Medicines during Pregnancy Registry. Temple University, with Vince Armenti [ph] has the National Transplantation Pregnancy Registry. This registry is unique in that it enrolls female patients exposed to drug, as well as male patients exposed to drugs.

[Slide.]

So, when would it be best to establish a registry? It is probably most frequently done and certainly most feasible when a product is first marketed either as part of the Phase IV or voluntarily on the part of a company.

It could also be done at any time if there seems to be a need for increased data.

Another reason to establish one might be if there is an new indication or a new dosage form that may indicate that this product might be used in pregnant women or women or reproductive age although I have no examples of drugs that this has happened to.

[Slide.]

There are certainly pharmaceutical products that would make good candidates for pregnancy exposure registries, certainly, any

product that would be used in pregnant women for conditions that require treatment.

I also talked about the inadvertent exposure with unplanned pregnancies, so products that would be likely to be used by women of childbearing potential.

Another example would be products that would be used over conventional therapies that are known to be teratogenic. So, I will give you an example here, is the drug called Amevive or alefacept. This product was approved I believe approximately two years ago for the treatment of chronic plaque psoriasis. The animal reproductive toxicology data for this product were clean meaning there was no teratogenic finding. So, this product got a pregnancy category B.

This product was discussed at Advisory Committee and several members of the Advisory Committee brought up a concern that this product

would probably be used preferentially over standard treatments for chronic plaque psoriasis, because those treatments are methotrexate, systemic retinoid, which we know are human teratogens.

Other good candidates would be live-attenuated virus vaccines. We know that viral exposure during pregnancy is very bad on the fetus.

[Slide.]

Interestingly, one of the questions that was asked yesterday afternoon was, okay, we have these systems, how have the data been used, how has the use of the data impacted on patient care.

So, here are a couple of examples. The data from pregnancy exposure registries can be used, and has been used, to change the pregnancy letter category. For those of you who don't take care of pregnant women or are involved in this area, the pregnancy letter category has a huge impact on the selection of drug use during pregnancy.

There are three examples on this slide. The first is Zovirax or acyclovir. The data from

this registry changed the pregnancy category from a C to a B. This registry was a joint effort between Burroughs Wellcome and CDC, and Elizabeth Andrews can probably talk about this more than I.

The registry ran for over 15 years and what I draw your attention to is that it took that long to enroll approximately 750 pregnancies.

Another example is Pulmicort or budesonide. As a matter of fact, all of the budesonide inhalation products have been changed from a C to a B, largely as a result of this Swedish medical birth registry data of over 2,000 births.

The third example is Sustiva or efavirenz, which is a product used to treat HIV. Here, we see a converse situation where the category was changed from C to D. This was data from the Antiretroviral Pregnancy Registry, and the occurrence of neural tube defects in a little over 100 pregnancies that were exposed led to this change.

[Slide.]

The data from registries can be summarized

in the Pregnancy Section of the label. The reason why this is important is because the Pregnancy Section of the label for the vast majority of drug products has only animal data, and most clinicians do not know how to use animal data to treat pregnant women, so having human data in the label is very important.

Data from registries can also provide a signal that requires or may require further investigation. An example is the Bupropion Pregnancy Registry.

In one of their last public reports on this registry, the Scientific Advisory Committee noted that there was the repeated occurrence of heart defects, and that committee agreed with a plan for more rapid methods of accumulating data and the monitoring of pregnancy exposure to Bupropion has been intensified, and this is under further investigation.

[Slide.]

There are certain benefits from conducting pregnancy exposure registries and from the data

that result from such registries. They are an important step in building prospective human data sets on pregnancy exposures and infant outcomes, but they are really just a starting place to get a handle on fetal risks. The registries can monitor for suspected effects and the registries can identify factors that may affect risk.

Registries can provide an estimate of increased risk of birth defects over background.

[Slide.]

But they also have the potential to establish broad margins of safety and provide reassurance regarding the lack of fetal risk, which is very important in pregnancy.

The most important thing that pregnancy registries can do is provide clinically relevant human data, data that is useful in making decisions for treatment in pregnancy and data that are useful for counseling pregnant women about inadvertent exposures.

[Slide.]

But there certainly are limitations to

pregnancy exposure registries like there are to any type of study. Pregnancy exposure registries are really best suited for major teratogens. It is very useful to be able to say that a drug product is not another thalidomide.

[Slide.]

But they have limited ability to pick up more modest teratogens or an effect that is much less frequent. They have limited ability to look at the teratogenic effects on a specific organ system or a specific defect. This really just boils down to numbers and power.

They have limited ability to detect an increase in spontaneous abortions, and they also have limited ability to detect outcomes that manifest late after birth, such as behavioral development, intellectual development, reproductive function, something that was alluded to in Dr. DalPan's presentation this morning, as well.

[Slide.]

You saw the variety of registries although certainly not a comprehensive list, so one could

easily envision patients who are taking multiple drugs that might be candidates for multiple registries.

This would be extremely burdensome and time-consuming on the part of the patient, on the part of the practitioner, and also makes attribution of risk across studies quite challenging, and as you saw with the acyclovir case, it may take a long time to collect enough exposures.

[Slide.]

There are numerous challenges to these type of studies. This is certainly not a comprehensive list, but some of the methodologic challenges include the sample size, how big is big enough when you have data at the end, was it big enough, are we comfortable with this.

When the sample size is calculated, another question is, is it feasible to try and enroll or to think that you might be able to enroll that number of women.

There are data capture procedure

challenges, who provides the source of information, is it the information on exposure, the information on outcome? Is it the mother, is it her OB? Is it her neurologist? So, you can see that there would certainly be challenges in that.

What is the outcome of interest, and how long will there be follow-up in this study?

Certainly, another methodologic challenge is the selection of the comparison group or groups, would it be an internal group, an external group, or a combination of both.

[Slide.]

There are certainly broader challenges to conducting these type of studies. The issue or IRB review, informed consent documents. The whole patient privacy issue becomes a big factor in these type of studies.

What is the role of the independent data monitoring committee or a scientific advisory committee?

When there are international registries, one of the issues of discussion is the

heterogeneity of the data across multiple countries.

Another issue is the data release criteria, are there prespecified data release or will there be an annual report. Then, when should you discontinue the registry.

[Slide.]

I already mentioned the challenges about nomenclature, and I think that is something to really consider as you have your discussions.

I mentioned the issue of generic manufacturers. It is certainly something to consider, as well.

There is also the issue about if there is a signal, how should that be pursued, how should that be worked up.

When the issue of pregnancy and drugs are talked about, there is a tremendous amount of discomfort, and there is definitely discomfort and inexperience with using this type of data, as well.

[Slide.]

So, in summary, and to end my presentation

this morning, there is no single methodology to assess the complete teratogenic effects of a drug.

Pregnancy exposure registries are an important component of overall postmarketing surveillance of the safety of drug use during pregnancy, but this is only one tool, it is useful, but it is not a perfect tool. It is a place to start, and this is not a comprehensive systematic approach. It is really a one-drug-at-a-time approach.

Thank you.

DR. GROSS: Thanks very much, Dr. Uhl.

The next speaker will be Dr. David Graham of the Office of Drug Safety, who will discuss Population-Based Epidemiologic Safety Studies: Overview and Challenges.

Population-Based Epidemiologic Safety Studies: Overview and Challenges

DR. GRAHAM: Good morning.

Today, I will talk about population-based epidemiologic safety studies as we have attacked them at FDA. This will be a high-altitude

overview, trying to emphasize some of the challenges we face in seeking your input on how we can tackle those challenges.

[Slide.]

The first question just to sort of set the background, why might we want to do postmarketing safety studies in a population-based setting?

There may be residual uncertainty at the time of approval and typically, if that residual concern is great enough, a company might be asked to do what is called a Phase IV study, a Phase IV commitment in which in exchange for the drug being approved at that time, the company commits to doing a safety study. One could debate whether that is a good thing or a bad thing.

There could also be new safety signals that arise post-approval, and we discussed yesterday how those signals can be developed. Some of those signals might relate to things that are rare and serious, but they might be common and serious, so the question is how do you get beyond case reports.

So, that's I think what the focus of our program has been, is an effort to get beyond the case reports.

So, what are the criteria one might use to decide what to study? We have looked at it in terms of what is the impact on patients, and so we focus our efforts on things that are serious, so basically, things that might land you in the hospital or land you in a cemetery.

If it is potentially a large exposure, that becomes a consideration, as well, because the potential to magnify a risk across a broad population is also important. If the excess risk is potentially large, so we are talking about a very great relative risk, that is another way that the impact on a population could be magnified especially if the drug use is extensive, as well.

If you have safer alternatives, well, then, now we have the question of sort of in the grand scheme of things, does it make sense to use one drug that perhaps has a high negative impact on the population when there is an alternative or

alternatives that don't have that negative impact.

Then, what about the situation when we are dealing with a drug that isn't used for a particularly serious indication?

Finally, we have the whole area of off-label use, inappropriate off-label use, and that can have a great impact in terms of population harm.

[Slide.]

This slide graphically displays the approaches that we have at our disposal to do postmarketing safety studies. The top two, the Phase IV commitment that I discussed before, ad hoc postmarketing studies, these would be studies that occur once a drug is on the market and some safety question that was unanticipated or was not recognized at the time of approval pops up later on, and so on an ad hoc basis, a study is performed.

These are things that can be done by the company. The Phase IV studies, if they are done, are always done by the companies.

We then have what we can do in the Office of Drug Safety. In this capacity, they have traditionally all been ad hoc types of studies. We

can use national data that are collected through various surveys that the Government sponsors. We have a Cooperative Agreement Program, which is a grants program, and I will describe that in a minute, that gives us a limited capacity to do population-based research.

We have recently acquired the General Practice Research Database, and we heard a little bit about that yesterday, and I will talk more about it.

Then, we have had a couple of special projects. These have sort of been one- or two-time endeavors with Kaiser Permanente in California and with the Veterans Administration. I will describe those, as well.

[Slide.]

Among the National Data Resources that we have used within our office, we have NHANES, which is a large, population-based physical examination

survey that is conducted on a periodic basis, and we use this to do a study of QT prolongation in the general population and to look at the prevalence of use of drugs that might interfere with the metabolism of other drugs that could cause QT prolongation to occur.

We have used data from the National Hospital Discharge Survey to get background rates for incidence for disorders that are difficult to obtain background rates for, such as pancreatitis in children or acute myocardial infarction in children.

The National Ambulatory Medical Care Survey is conducted I think on an annual basis. There is about a two-year lag in the data that comes from it, but one can get measures of prevalence of drug therapy and prevalence of diagnosed disease conditions, and we have used this from time to time, but a better source of data for us we believe is the drug use databases that Judy Staffa had talked about yesterday.

Then, we use statistics from the Census

Bureau and other National Center for Health Statistics to bet various denominators that we could use for various research purposes.

These types of data can be used in conjunction with case reports to help refine a signal, get a sense of whether what you are looking at is possibly something that needs to be followed up more closely.

[Slide.]

Among the population-based resources that we have at our disposal, this slide outlines our current armamentarium, and you will see the particular program that we have access to, the population size, and number of years of data that those resources are able to provide in a longitudinal basis.

Here, at the bottom, I have a question next to Medicare. Yesterday, there was a lot of enthusiastic discussion about the possibilities when Part D, the prescription drug benefit, is implemented beginning next year, and using that for an enormous database that one could do spectacular

studies in.

We have done some preliminary work here and that is why the question mark. The databases that exist with Medicare right now are enormous. They are not structured to do research in and getting one database to talk to another database is incredibly difficult.

The amount of computing resources that are required to bring these databases together is also enormous, and now we superimpose upon that a large drug benefit program, and depending on how it is designed, could have great implications for what its utility is.

So, I have questions there about sort of I don't think the Committee should expect that in the near future this is going to be a resource that is readily available for research purposes.

[Slide.]

The basic features of population-based databases are summarized on this slide. First, they are population based, and the advantage that gives us is that we have a defined population, we

know where the cases are arising from, where the exposures are occurring, and theoretically, we have the potential to count all the exposures and all the outcomes, and that, from a scientific perspective, is a very powerful advantage.

They are large and "large" is in quotations because large is never large enough, so we have these databases and we call them large, but we are always coming up against problems and questions that we realize, well, this database really isn't large enough.

Where this question of large enough comes about is it has to do with the negative study. What do you do with a study where you find there the relative risk is 1.5, so we have a 50 percent increase in risk, but the confidence interval includes one which says there is possibly no real increase in the risk.

Well do you have a problem or don't you? Oftentimes, this is the result of power, and it is a result of the size of the database. So, from my perspective, that is an important consideration for

the future.

They are longitudinal in nature, which means they follow patients over time, and that is the whole notion of the Roman cohort, that you are just marching these people through time.

They are typically automated, which means that pharmacy records, provider encounters, procedures, and all, are automatically captured and computerized, so theoretically, they are available for research purposes, and then all of them have a capacity to get back to primary medical records, which is important for outcome validation and possibly for other applications, as well.

[Slide.]

This is just to give you an idea of how much FDA currently spends on the data resources that I have talked about. Other components of the government fund the national resources, so they supply us with the CDs for free, so that doesn't cost us anything but time, so that is a real bargain.

A Cooperative Agreement Program, we spend

about $900,000 per year and for what we get from it, I would say that that is a real bargain, as well. You can talk to anyone who is involved in any of these research programs from a couple of slides before, and ask them how much did they get from NIH to perform a typical epidemiologic study, and you will find out that what they typically get, or if they do a study for companies, how much they typically get, and you will see that this amount that gets spread over three programs is less than probably what one study costs, so from the government's perspective, this has turned out to be a real bargain.

The General Practice Research Database, we just acquired it at the end of last year, and we spend about a half a million dollars a year on that. That is just for the license to access the data.

Then, for the special projects that I described, the VA medical system, I will describe in a moment, the programs, studies that we have done there, they cost us about $10,000, and the

Kaiser Permanente study that we did on cardiovascular risk with NSAIDs, we contributed $60,000. Kaiser probably contributed about a quarter of a million dollars in terms of time and resources to completion of that study.

Then, with Medicare, this could be extremely expensive, at least based on our preliminary investigation. We are in conversations with people from Medicare CMS, and we recently submitted to them some study proposals to do simple studies using a component of data that is called Part B. Part B data is data on drug administrations by physicians in their offices, so this would be parenteral, intravenous, intramuscular types of things.

We wanted to do simple, what we would call feasibility studies, how many people have gotten treated with this particular drug, and how many of them, anytime in the history that you have available on computers did they have particular sets of outcomes.

The cost estimates we got back to do that

simple study were about $60,000 for a single. Now, I can tell you in the Cooperative Agreement Program, we do those probably, I mean I don't know what the actual cost is, it is probably for a thousand dollars, or a couple thousand dollars, in terms of how easy and quickly that it can be done.

So, you can kind of see the enormous gap in costs between using sort of a large Medicare system that was designed in an age before people were thinking about research purposes, and using other research databases where people who are experiencing research have worked with them to get them into a condition where they can be used in an efficient manner.

[Slide.]

Over the next few slides, I will describe in a little bit of detail the different components from the previous slides.

Our Cooperative Agreement Program gives us access to three population-based databases which hear research expertise attached to them, so we are not only in a sense gaining access to databases,

but we are gaining access to the research expertise behind those databases. So, those would be like your principal investigators.

These are longitudinal and they give us the ability to examine patterns of drug use within that database, exposure-outcome relationships, and we can study the effects of regulatory intervention on physician and patient behavior and outcomes.

An important limitation of these databases is that there is no routine ascertainment of death, so there is not, in a reliable way, ascertainment of death in these databases as a rule. There are exceptions, but generally speaking, healthcare administrative databases, all they are interested in are you a member, are you eligible for coverage or are you not, and if you disappear from the database, well, maybe that is because your job changed, maybe that's because you moved away, maybe that is because the company you work for changed insurance carriers, maybe it's because you died.

Unfortunately, death is a very hard outcome which from epidemiologic perspective, is a

very desirable outcome, not that we want people to die, but it is easier to study if you can measure it.

[Slide.]

Now, the quality of the data that we get from these record-linked, insurance-based systems, is variable. The pharmacy claims has very high validity and in terms of data lag, most of the claims are in the system pretty quickly.

For the diagnosis claims, if you are looking at outpatients, if you want to go to an outpatient setting and get the medical records to validate claims, the validity is generally low.

For inpatient claims, it really depends, and there have been a number of studies that have been done looking at particular outcomes where it is known that the positive predictive value of a hospital-based claim is extremely high. Myocardial infarction is an example of that where the positive predictive value of a hospitalized claim in one of these databases is in excess of 90 percent.

One of the disadvantages, if you will, or

limitations is that to have basically complete ascertainment of the diagnoses of the outcomes, if you will, it is generally in the neighborhood of about 6 months before all of those claims get processed and into the system.

It's sort of a front-ended, skewed normal distribution curve where a lot of the claims come in, in the first several months, but then you have this long trailing tail that goes out to six months.

For procedure claims, generally, the validity is high because these are expensive and so they are audited pretty well, and they have a completion rate that is pretty similar to that of diagnosis claims.

So, this in a sense gives you a sense of, if you are going to use these databases, how current can the studies that you are going to do be and sort of what time considerations you have to take into consideration when you are planning your study.

[Slide.]

Now, we are in the midst of changing the way we fund our Cooperative Agreement Program. For the last 15 years or so, it was a cooperative

agreement, it was basically a grant, and we are shifting now to a contract mechanism. Associated with that, we anticipate there will be growing pains and challenges in working with a new funding mechanism.

We have an intention to fund multiple databases. The focus, of course, would be on safety-related issues that are important to the FDA, and we are hoping to retain the collaborative relationship that we had within the Cooperative Agreement Program.

One of the real strengths from our perspective with the Cooperative Agreement Program was that FDA epidemiologists worked as equal partners with the researchers in the databases that were funded to do epidemiologic studies, so it contributes in a sense a unique FDA perspective, but it gives our epidemiologists an opportunity to in a sense be mentored and trained by very

accomplished epidemiologists, so it really in a sense is a quality improvement process within FDA.

[Slide.]

The next database to discuss is the General Practice Research Database, and this was mentioned briefly yesterday.

It is a United Kingdom-based electronic medical record system that is focused on the general practitioner. This system works well in the United Kingdom because the GP is the gatekeeper for all healthcare. In the United States, within certain healthcare environments, a system like this is workable, but in other environments, it might not be as workable because of the fragmentation of healthcare in the United States.

In the United States we have, in the databases we talked about, relatively high turnover. The turnover can be as great as 20 percent per year. What that means is if you want to follow a patient longitudinally over time, that you are going to have dropout because people are changing their insurance carriers and the like.

In the GPRD, turnover is lower because the UK population is less mobile than in the U.S. It captures GP visits, health measures, blood

pressure, cholesterol measure, weight, body mass index.

We are in the process now of doing a data quality analysis to see sort of what is the completion rate for different components of these health measures, but the appeal of them is that you can get access to variables that aren't routinely available in the more automated health claims data that we work with in a Cooperative Agreement Program.

It gets consultant referrals and hospitalizations. You can get laboratory and procedures, the fact that they occurred, but also, in some cases, the results, and that is very attractive, as well.

The way these systems work, the patient comes into the physician's office. The physician has a paperless medical record. Everything or almost everything is in the computer, and when they

go to issue a prescription, they type it into the computer. The prescription comes out, they give it to the patient, but that information if now recorded in the computer and it is sent to a centralized database.

The system is also very good at ascertaining death although there is at least four different places in the database where the fact of death can be recorded, and they have different levels of validity and different time sequences of when the data gets entered into that variable, and so that creates complexities of its own.

In any event, it's an enormous database, it has a very complex relational structure, and that poses challenges. For us, we have in-house access via the internet, so that is very attractive. It gives us a natural database in-house to work with.

[Slide.]

The unique limitations, though, are that this is a UK population not a U.S. population. That may or may not be important depending on the

question. They have a national formulary which really focuses on cost containment, and the physicians are trained not to prescribe the latest, greatest, most expensive drug on the market if there is something else out there that costs about a tenth of the cost and does the same thing.

So, for new molecular entities, where you might have particular concerns or interests, it may take a while before the market penetration, so to speak, into the database gets high enough to do a credible study.

There are different standards of practice and different modes of practice in the UK from the United States, and that has to be taken into account, as well. Just one example. Attention deficit disorder that affects anywhere between 6 and 25 percent of kids in the United States, depending on who you reach, is a diagnosis that does not exist in the United Kingdom.

So, does that mean that kids in the UK don't have attention deficit disorder? I don't know. Maybe in the U.S. we don't, maybe it's just

bad behavior, but the fact is that they have got different ways of doing things and if you are not aware of what those are, you could sort of go down a wrong pathway.

As a said, they are very large files, so that does impose limitations and challenges to us, having the proper amount of computer hardware to download these files, to have the right types of personnel in terms of programmers and the like to work with these data are thing that we struggle with, because we spend half a million dollars on the database, but then because of the way government is with personnel ceilings, you can't hire a programmer.

So, you spend a half a million dollars on the database, and you can't sort of get an extra programmer to work on it. So, those are the types of conundrums that, well, I face it, but only as a scientist. Paul and Anne, they face it as sort of the managers who listen to use carp and complain that this is ridiculous.

[Slide.]

Now, other population-based resources that we have access to are the VA medical system. What is attractive about that is that, well, it has

about 3 1/2 million active members. In the database, over time, there is probably about 12 million people.

It is the largest single repository of HIV-infected patients in the world, and it's moving to an electronic medical record. It is broken down into these sectors around the country, and some of those sectors are computerized and other aren't, but eventually, the goal is to have the entire system computerized.

It is an unusual population, you know, males, they are generally older, and they are generally sicker. One of the big limitations, though, is that if you are dealing with an acute outcome, an acute hospitalization, and you don't happen to live near a VA hospital, the VA probably is not going to know that you are hospitalized, so that becomes a real issue.

Another attraction to the database,

however, is that some of the laboratory data is actually computerized and on line now. We have done two studies with this database. One was looking at hypoglycemia with fluoroquinolone antibiotics, and the second study is looking at the occurrence of osteonecrosis primarily of the hip, but of other bones, as well, and patients with HIV infection treated with HIV antiviral drugs, and looking to see what the relationship is between the incidence and prevalence of osteonecrosis and the types of antiretroviral therapy that patients were receiving in trying to disentangle is this issue which is emerging as a concern in the HIV community, is this a result of living longer with HIV or is it possibly a result of particular classes of antiretrovirals or combinations of use of antiretrovirals.

So, that is a very exciting study, but as you can imagine, we are the mercy of the people in the VA in terms of they have access to this very confidential database, so the primary researcher we were working with there has lots of other

responsibilities, so this study has moved very slowly, but it is moving forward and we are very excited about it.

Kaiser Permanente is a very large HMO and it is a closed, integrated healthcare system, so if a patient needs to be hospitalized, typically, they are hospitalized at a Kaiser hospital. If they happen to be hospitalized at a hospital outside of the Kaiser system, the next day they are shipped to a Kaiser hospital unless they are medically unstable, and there is good cost reimbursement.

You would think that, well, at the VA, we should be able to access these missed hospitalizations because the VA is going to pay for them. It turns out that the VA doesn't do a very good job of cost accounting, and so the reimbursement files are a shambles, and really can't be used to identify hospitalizations that are missed.

Kaiser isn't as inefficient, so you are able to access those. They have some formulary restrictions. They have a lot of laboratory data

that is computerized, and they ascertain death. We use this system to do a study of cardiovascular risk with NSAIDs, and that was published in Lancet earlier this year.

[Slide.]

This summarizes sort of the spectrum of studies that we have done using the resources I have just described. They go from looking at patterns of drug use, persistency of use, which can be an important question, and I will just sort of pose this to you.

About three years ago, colleagues and I did a study looking at the prescription use of a weight loss reduction drug. Well, morbid obesity is a chronic condition, so you would expect you should be treated chronically for it if the drug is going to work.

Well, we found that the typical duration of use of this anti-obesity drug was less than 30 days, so the question one raises is the question we raise is, well, what sense does it make to have this drug that has toxicity, that has a definite

identifiable toxicity, if no one is going to use it long enough to obtain a benefit, but they are all going to use it long enough to potentially obtain some risk.

We also use it to identify patterns of co-prescribing for contraindicated drugs, drugs that might interact.

Case series. We have used this to identify actual cases, so that we can do follow-back. We have done this in the field of--I am looking for the association of particular drug exposures to birth defects, and then the various methods of epidemiology that are pretty standard.

Within the Kaiser system, we were able to go back and do patient surveys to get information that wasn't in medical or claims data that allowed us to determine whether or not there were unmeasured confounders in our data, and the hope would be that other studies like other surveys like this of patients, of physicians, might be possible in other databases, as well.

[Slide.]

This slide just summarizes some of the studies that we have done over time, and I don't think I need to focus too much on that.

This last study here was the first example where we looked to see what was the effect of FDA regulatory action on physician behavior, and what we learned was that there was basically no impact, very little impact.

[Slide.]

As promising as these databases appear, there are a host of limitations, potential limitations to their use. People who have worked with these, they will be very familiar with this slide. For those of you who maybe haven't worked with it, maybe some of it will be new information.

Common to almost all of these databases are that they deal with outpatient prescriptions only, so if you go into the hospital, that becomes a black box. You face the problem of market penetration, how quickly is a new drug taken up into that database and what is the extent of use, and that will determine at what point in time you

might be able to launch a study.

Sample size is always a question. OTC and herbal and alternative drug products generally aren't captured. We talked about the data time lag. If you want to look at special populations, these general population databases may not have large numbers.

If your database is one that is tied to employer-based health insurance, well, you are going to have a paucity of people over the age of 65, because most people retire before that age.

You have issues of privacy and then completion time. What I mean here is it is how long it takes to do an in-depth study, but that is a problem that is common to all research.

Now, specific to some databases are that they may be insurance based, they may have particular formulary issues. That would mean a drug is or isn't available. There may be tiered co-pays, so that if their co-pay is too high, either people won't use the drug or you might miss capturing the drug.

We talked about patient turnover. Most databases don't have lab results, and they don't ascertain death.

[Slide.]

The last two slides are sort of a summary of the challenges that we face and sort of I suppose in a sense, the types of things we are asking you to consider in your deliberations.

You know, we face budgetary constraints. These databases are expensive. You have seen how much we fund them for. For those of you who are researchers, you realize that our funding level is pretty paltry. We admit that, but it is as best as we have been able to do.

Our managers have been pretty good about preserving this in an era where things are being cut left and right in government.

Then, the operation of these databases in terms of how do the databases work and how do we work with them. Infrastructure within the Office of Drug Safety, how should that be configured? I mean we have a number of epidemiologists.

We really don't have people who are dedicated programmers. If you think of people who are involved in research, how is your research organization structured and the types of people that you have, informing us about that and the right mix might be very useful in guiding our

managers in terms of what they should lobby for, in terms of personnel.

Then, we have training and hardware and software requirements. Downloading a database from the GPRD doesn't work on a typical PC, and that is what we have. We have typical PCs. So, now we want to get something bigger. Well, we found money to do that, but when we get these other databases in, we are going to have increased infrastructure requirements.

Then, there is methodologic concerns, study design, what are the proper covariates, the power, but these are scientific issues, but they are challenges nonetheless.

[Slide.]

What topics should we study? You know, we

talked a little bit about topic identification. That has been I think a lot of what day 1 was talking about. How do we select among all those? Which are the ones that should go on to this type of investment?

How do we match the question with the appropriate data resource? How do we prioritize them? Then, what applications should this have? Should they be solely guided by the need to put something in a label to take a regulatory action? Should they also include things that have a larger public health goal that might not be something that is immediately of a regulatory concern?

These, I think are things for the Committee to consider.

Thank you very much.

DR. GROSS: Thanks very much, David.

I think at this point in the morning we are going to shift our 10-minute break to now, so we will take a 10-minute break now.

[Break.]

DR. GROSS: The next speaker will be Dr.

Gretchen Dieck, who is Vice President, Management Strategy, Worldwide Development, at Pfizer. She will talk about postmarketing studies from the Industry point of view.

Postmarketing Studies from the Industry Perspective

DR. DIECK: Thank you, Mr. Chairman.

It is a pleasure to speak with you today and to give you the industry perspective on postmarketing studies. I am the current Chair of the PhRMA Pharmacovigilance and Epidemiology Technical Group.

Although we are eagerly interested in the area of drug safety and improving tools for pharmacovigilance, we didn't have enough time to put together collective comments, so I am speaking here on behalf of my own company Pfizer where I am head of Risk Management Strategy.

[Slide.]

In order to set the framework for my talk, I would like to remind the Committee of some key risk management assumptions. First, each drug is unique and presents its own balance of benefit and

risk. Second, no drug is risk-free and sometimes we forget this, that even the safest drugs do present some risks for certain individuals.

It is important that safety-related decisions, such as labeling changes or access to drugs be based on science-based evidence, and I feel very strongly that it is industry's responsibility to bring some of this science to the table in order to support the other tools, which are primarily clinical trials and spontaneous reports, and some of the other types of tools we heard about yesterday, active surveillance, and so forth.

No individual source of information should be considered in isolation. All of these tools are a piece of the puzzle. Finally, a key to effective risk management is good communication with both the regulators and the medical community, and this helps ensure patient safety and minimize the likelihood of surprises. I will give some examples of what I consider good communication with regulators and some of the studies that we have

carried out.

[Slide.]

Although we are focusing on the post-approval time period, I am taking this opportunity to make my plea that good risk management really occurs early in the drug's lifecycle and follows the entire life of the drug.

There are many activities and studies that can be carried out pre-approval using some of these methods I will discuss today, and we can identify subgroups at risk or we can understand the patient population better.

If you start thinking about risk management at the time of approval, in my opinion, it is too late.

[Slide.]

You have heard a lot about these different tools both yesterday and today. Post-approval studies frequently in the form of observational epidemiological studies complement the clinical trials and the spontaneous reporting system in rounding out our safety profile of a drug, and this

graphic simply shows them in decreasing order of scientific rigor.

You have the gold standard clinical trials at the top, followed by epidemiology, which still uses the scientific framework, and then the spontaneous reports, which are primarily signal detecting.

[Slide.]

When a drug is first approved, it has usually been studied in 3- to 10,000 patients, although I think 10,000 patients is considered a pretty large clinical development program. Usually, they would be a little bit smaller than that, and we have a basic understanding of commonly occurring adverse events without a great deal of granularity in the spectrum, so you can identify risks as small as 1 per 1,000, and you have some of your basic commonly occurring events, but the public expectation is that we have the knowledge as if we had studied the drug in a million patients where we can identify very rare adverse events, and we have a lot of granularity about the types and

spectrum of adverse events.

How do we get from the reality of what we know at approval to what the public expects in approval?

[Slide.]

What we do is we build that knowledge over time and before approval, we can complement the clinical trial with background epidemiological studies of the disease under study, and when the drug is approved, we can start getting information from spontaneous reports about rare events, and so you are identifying things a little bit more rarely here.

Then, you can carry out observational studies, which is really the focus of my talk here, and then sometimes the observational studies may take you back to the lab or the clinic to do other types of studies. This happened with our drug Viagra, where there was a question of its cardiac safety after the drug was approved.

We went back and did hemodynamic studies, which gave us a lot of information about what

happens in cardiac patients taking Viagra and what happens to their hemodynamics of the individual.

Even if we doubled or tripled the size of the clinical development program, so that you had 30,000 to 50,000 patients, it is still insufficient to identify really rare events. The reality of the situation is we can learn a lot before approval, but there are certain things that we can only find after the drug has been put on the market.

[Slide.]

Issues that may arise in the review period for a drug include whether there is a specific risk issue, what are the characteristics of the population being treated, and how can adverse events received in the immediate post-approval period be put into context.

An important goal of risk assessment is to identify subgroups of patients that may be higher risk, so that this information can be communicated to prescribing physicians, and that this is key to ensuring patient safety by identify subgroups at risk.

We have heard a lot about risk in general, but by identifying subgroups at risk, you have identified those patients that can safely take the

drug and allow them to continue taking the drug safely, and you have identified patients that probably shouldn't take the drug, and that information can be communicated to prescribing physicians, and that is an important part of what we do.

[Slide.]

There are several tools that we traditionally use to carry out post-approval studies. You heard some excellent descriptions this morning of the classical epidemiological designs, the cohort and case control, and I am certainly not going to go over those.

We also use something called the large, simple trial, which I will describe a little bit, and I have just a brief conversation about some of the things that we do with registries.

Because observational studies are not as strong methodologically as clinical trials, it is

important to validate the studies using various study designs and study populations, so we often will have a risk question, and we will do several different studies using several different databases or populations to try and validate the findings.

This is very important and I have some examples of where we have done that.

[Slide.]

As I mentioned, one of the purposes of post-approval studies is risk assessment, was one of its bread-and-butter responsibilities, and to see if there is an increased risk relatively of an event compared to another drug or compared to general background incidence.

One example of this type of risk assessment can be shown with Geodon, an atypical antipsychotic drug that was approved in the U.S. to treat schizophrenia in early 2001. Geodon had been shown in the clinical development program to have a moderate degree of QT prolongation, which can in some instances lead to something called torsade de pointes and sudden death. Although we didn't see

those outcomes in our clinical trials, it was a theoretical risk that needed to be evaluated.

So, the risk that we asked was whether or not QT prolongation resulted in greater incidence of cardiac death or hospitalization due to cardiac events.

[Slide.]

So, we designed a large, simple trial to look at this particular question and what we wanted to look at were cardiovascular events in real life observational setting, so a large, simple trial is a study that is observational in nature beyond that initial randomization to treatment. It is not interventional.

The patients were randomized to either ziprasidone, which is Geodon, or olanzapine, another atypical antipsychotic, and this randomization ensures that the patient groups are similar and also controls for channeling bias, which means that if a physician would for various reasons either the patient's medical history or his just gut feel about the patient would

systematically channel the patient to one drug versus another. That is why we didn't use the regular cohort, we used the randomization to control for this.

So, that allows the patients to be as similar as possible and controls for all sorts of types of bias.

18,000 patients are targeted to be enrolled in the study and followed up for usual care, and I do want to mention at this point that that is a challenge in itself, because this is a schizophrenic population and that has its own challenges in terms of follow-up.

[Slide.]

Why do we choose a large, simple trial? First, it's the strongest of the observational study designs, and the process of randomization, as I mentioned, controls for many types of bias including both measurable and non-measurable, including confounding by indication and channeling bias.

This tight control of bias also allow us

to have sufficient power to detect a smaller relative risk than classical epidemiological studies, and this particular study is powered to identify minimum relative risk of 1.5.

Second, the large, simple trial allowed us to set up independent governance structure that ensured the highest standards of the conduct of the study. As you can see, we have a Scientific Steering Committee, we have a Data Safety Monitoring Board, and we have an Endpoint Committee, and these committees all independently monitor the study.

The study is currently in progress and the first patient was enrolled in early 2002. We had initially planned to do the study in three countries - the U.S., Brazil, and Sweden, but we had tremendous recruitment problems. I will discuss this a little bit more when I get to challenges of doing these types of studies.

To date, we have enrolled almost 14,000 of the 18,000 patients needed for the study, and we had to go into 15 countries, and we have another 3

countries that we are going to go into for a total of 18 countries, and we are carrying it out at 450 different sites. So, this is a large de novo study that we have set up and are carrying out, and a lot of effort has gone into this study. I will get back to that in a moment.

[Slide.]

Another purpose of post-approval studies is understanding the population being treated. This gives us a greater understanding about the natural history of the disease. Although I have categorized these types of studies as post-approval, these studies could easily be done pre-approval, either started or completely carried out.

In some instances, when we want to know more about the population being treated, and we know we are having an advisory committee, it is very useful to have this type of information available for advisory committees to review.

The example that I would like to discuss pertains to our anti-migraine medication of the

triptan class called Relpax. Due to a vasoconstrictive effect among triptan, a safety hypothesis emerged as to whether or not triptan use was associated with great cardiovascular disease, morbidity or mortality.

We carried out two epidemiological studies. These are database studies, such as Dr. Graham was discussing. We used the General Practice Research Database, which he gave you an indication of what is involved with that particular database, and it's in the UK. We used the United Healthcare Research Database in the U.S.

I will only present the results of one study, because the results of the other were very similar.

[Slide.]

The design was that of a retrospective cohort study using United Healthcare data from 1995 to 1999, and all patients with diagnosis of migraine or who have been dispensed a triptan were eligible for inclusion in the study, and non-migraine controls were age, sex, and healthplan

matched 1 to 1.

Of the over 130,000 migraine patients that were identified, approximately 50,000 were on triptan and approximately 80,000 were non-triptan users.

[Slide.]

I don't know how this is going to project, but I will go through the slide quickly. It graphically shows the rates of vascular events and mortality among those with migraine compared to those without. So, the events, over here we have MI/stroke, serious ventricular arrhythmia, unstable angina, TIA, cardiovascular mortality, and all-cause mortality.

This is 1. These are point estimates with 95 percent confidence intervals. We are comparing migraineurs to non-migraineurs regardless of treatment.

What we can see is that migraineurs were significantly more likely to experience stroke, unstable angina, and transient ischemic attack than non-migraineurs. This tells us that migraine itself

is associated with certain conditions distinct from any drug effect. This information is very important when evaluating emergent safety information.

The next slide will be all migraine users and we are comparing those that used triptans to those that don't.

[Slide.]

With respect to those with migraine or here we have, these are pairwise, so for each of these events, MI/stroke, ventricular arrhythmias, unstable angina, TIA, and so forth the top one is current use versus non-use, current triptan use, and this is recent triptan use.

Here, you can see there is no evidence that recent or current triptan use is associated with any ischemic types of events, that not one of them was significantly on the righthand side of 1.

We did have a finding that unstable angina and all-cause mortality with current use did reach statistical significance, but we are not saying that triptan use is protective against these. All

we can conclude from this is that there is no evidence that triptan use itself is associated with an increase in any of these adverse events.

[Slide.]

The results of this study, and again it was replicated in another study in a different population, do suggest that triptan use is not associated with an increase in cardiovascular events, either morbidity or all-cause mortality, and it lets us know that people with migraine have an inherent risk of strokes, TIA, and unstable angina, and this has to be taken into consideration when you are evaluating risk when the patients are being treated.

[Slide.]

Another purpose of post-approval studies is to put adverse events in perspective. An example with triptan that we just discussed is one example, and also another example is with Geodon, again, an atypical antipsychotic.

Again, because of that QT prolongation and that theoretical use as to whether or not it could

end in clinical adverse cardiac events, we are interested in understanding the cardiovascular outcome in patients with schizophrenia and whether or not they also had an inherent risk of certain types of cardiovascular morbidity or sudden death.

This time we carried out three studies, one in Saskatchewan, Canada, one in the U.S., again using the United Healthcare database, and one in Sweden using information from the Swedish National Board of Health and Human Welfare, and the Swedish data were actually hospitalized patients whereas the other two databases were claims databases, such as have been discussed by Dr. Graham previously.

Again, I will only describe the results of one study. This was the Saskatchewan study, but the results of the other two were very similar.

[Slide.]

The study design was a retrospective cohort study, and we determined baseline prevalence of risk factors among schizophrenics diagnosed between 1994 and 1995, and we had an incidence period and follow-up between 1996 and 1999.

All of these studies, as well as the Relpax studies that I just described, have been published in peer-reviewed journals.

[Slide.]

The relative risk--this is morbidity--the relative risk of developing cardiovascular disease and diabetes among schizophrenics compared to non-schizophrenics during the follow-up period are displayed here, and you can see schizophrenics were significantly more likely to develop ventricular arrhythmias, strokes, and diabetes in this particular population.

[Slide.]

More interesting, looking at mortality, all ways that we looked at mortality, schizophrenics were more likely to have experienced some type of mortality compared to non-schizophrenics. We even split it up between suicide and non-suicide types of death, and among the non-suicide, we could break out sudden death and cardiovascular death. Again, they were all statistically significant.

All three studies concluded, very surprisingly, that schizophrenics, regardless of treatment, have a 3-fold increase risk of sudden death. Again, this type of information is very important and that it can be used as a framework to evaluate spontaneous reports of sudden death by

establishing a baseline level of risk.

So, this is the type of information that we could have available even before the drug is approved.

[Slide.]

The Relpax studies and the Geodon studies just described were carried out using automated databases which allow us to carry out studies relatively quickly, and because they did not evaluate a specific drug, at least in the examples that I gave you, they can be carried our prior to approval.

The Geodon large, simple trial was designed and implemented de novo. I mean obviously from what I was describing it is much more resource-intensive type of study, and it takes

longer to complete, and it is significantly more costly, but both types of studies using databases and carrying out studies de novo are very important because they give us different types of safety information and provides types of information that decisions could be made on.

[Slide.]

I just have a few comments on registry, and they are a little bit different than were presented previously, but very much complement what was said, as well.

Registries are another tool that we use to evaluate risk, and the most common type of registry that we have been participating with is the pregnancy exposure registry, but there are also registries, as you have heard, of other conditions like transplant registries, registries of serious skin diseases, and so forth.

Pregnancy exposure registries can be used to provide estimates of risk of adverse pregnancy outcomes. From my perspective, this information can be used by physician to help advise patients who

may have had a drug exposure during pregnancy if they have sufficient information, but because registries don't have a comparison group usually, my feeling is they are more useful as a signal-generating or signal-detecting tool as opposed to a hypothesis-testing tool.

However, as was also stated, if there is a know risk for the drug, registries can be very useful for giving you the spectrum of events that you may see from that exposure.

[Slide.]

Drugs that may benefit from pregnancy exposure registries include drugs that are likely to be used during pregnancy, such as antidepressants, drugs likely to be used by women of childbearing age, such as anti-migraine medication or systemic antifungal agents for vaginal yeast infections, drugs that have some indication of fetal toxicity, such as antiseizure medications, or new drugs for which the class of drugs is known to be teratogenic, such as vitamin A derivative.

[Slide.]

Here are some characteristics of the idea design for registry. I am not going to go through

these, because they were discussed earlier, but I do want to mention that Pfizer currently supports or works in conjunction with other companies and academic centers on a number of registries.

Three are pregnancy exposure registries, and some of these were actually mentioned in the previous talk. We are involved with the Anti-Epileptic Pregnancy Registry, the HIV Therapy Pregnancy Register, and we have a pregnancy registry on a drug for multiple sclerosis.

We are also supporting or working in conjunction with groups that carry out the registry as serious skin adverse events. That is called REGISCAR, and that is in Europe, and we have, working with another group, on a registry for familial adenomatous polyposis, which is a precursor to colon cancer.

We feel that there may be future opportunities to work more closely or to develop

other types of these disease-specific types of registries, and they could be a very interesting new tool to work with.

[Slide.]

Well, challenges, there are a couple of challenges that I wanted to go quickly through in carrying out some of these studies, but I think a lot of these challenges can be met in one way or another.

Post-approval, studies can present challenges which may impact their feasibility whether it is even possible to carry them out. One issue is recruitment rates of physicians and patients into studies that are set up de novo.

We had this challenge with our International Men's Health Study for Viagra where we were asking physicians to recruit 6,000 men into a study where we would follow up their sexual and cardiac health questionnaire.

We had tremendous problems both getting physicians to recruit the patients and to get the patients to fill out the questionnaire. One

problem was that we pre-tested our questionnaire up at Harvard where the School of Public Health Students were very happy to, you know, diligently fill out the questionnaire.

When we took it into France and Germany, we found that they thought that it was too long and men didn't want to answer questions about their sexual activity, and we did not pre-test the questionnaire optimally.

So, what we did is we carried out a survey, and we carried out the survey. We went back to physicians and we asked them why aren't you recruiting patients, what are the barriers to recruiting patients, and we went back to the patients and said what are the barriers for you for filling out this questionnaire. They had to fill out the questionnaire several times over a period of time.

As a result of that survey, we made a number of changes. One of them, we shortened the questionnaire and we took out ascending questions. We reimbursed them actually for their time to fill

out the questionnaire, and we addressed some of the concerns that the physicians had about the time it took them to recruit patients.

As a result of that, recruitment went up noticeably. With the large, simple trial for Geodon I mentioned, we also had tremendous recruitment problems, and again, thinking at first that we would only have to go into three countries, not really understanding--understanding theoretically that schizophrenic patients are hard to follow up, but not understanding the reality of that, and now we are going into 18 countries and all the infrastructure that you have to set up to be able to do that.

Each of these solutions is costly and time-consuming, but it made a difference in the success of the study, and these are the types of things, if you are really committed to carrying out these studies, and you have put a lot of investment into starting the study, it seems to me that these types of activities are very worthwhile.

In some instances, the risk question may

not be capable of being answered. With Relpax, the original risk question that we had was what is the risk of ischemic events in the migraine population treated with Relpax.

Well, I had given you examples of people with migraine or people on triptans in general, but people with Relpax, that's a relatively small number of people, and you are looking at a population of young women who not get migraines and they have a very low risk of this endpoint, and we calculated that we would need over 100,000 person years to be able to come up with that risk.

So, we talked to the regulators and came to an agreement that what we would do is an active follow-up of ischemic events that we got through the Adverse Event System, and that would be a more feasible way to answer that particular question.

Another example is for Viagra, the question was what is the risk of cardiovascular endpoints with Viagra alone. Well, in the real world, and in the clinical trials, too, I think, but in the real world, you rarely have someone take

Viagra without having or attempting to have sexual activity, and sexual activity has its own inherent risk for cardiovascular endpoints, and that has been well established.

So, we met with the regulators and we said we can't separate out the risk for Viagra alone because we have this other risk that is always in conjunction with it. So, we did, we met with the regulators and we agreed what the results of the study would be, the International Men's Health Study that we were going to be looking at this combination risk and what level of risk above the risk for sexual activity alone would be meaningful and would suggest that there was a problem.

This is an example where it is very, very important to meet with the regulators and we would get an understanding of what we can measure, how we can measure, and how we will interpret it, and do that before you carry out the study.

Another challenge that may be coming up is if you have a drug for smoking cessation, well, if that drug works, the patient will be going through

nicotine withdrawal, and how do you separate out the effects of nicotine withdrawal from a drug effect if you have a question about cardiovascular or whatever.

So, that is another example where we need to work with regulators about how are we going to be able to tease out these issues and answer some of these questions.

[Slide.]

In some instances, the risk questions that we get can't be answered using observational methods, and with Geodon, the original question was what is the risk of QT prolongation. Well, we couldn't do it observationally, because you need to Holter monitor to be able to test that, so what we did is we went back to the regulators and said, well, QT prolongation isn't really your concern, isn't your concern really clinical manifestations of that being hospitalization for cardiovascular disease and cardiovascular death, so can we change the outcome to that, and we can do that observationally, and they agreed that that made

sense.

Likewise, a question coming up on lung function where you have to measure lung function depending on how invasive that is, it could move you into a clinical trial or it could you move into thinking of a modified large, simple trial, you know, it's not classically observational methodology.

Other challenges of post-approval studies, particularly for those using automated databases, Dr. Graham went through these very nicely where you have missing information, past medical history, OTC use. That is a real problem. More and more as drugs go over the counter, it is very important for us to have them. So, we have a way around this limitation again is to do several studies using several different types of databases.

[Slide.]

Finally, in conclusion, post-approval studies are an important source of information that complement the clinical trials and spontaneous reports, and rounding out the safety profiles of

the drug, and pharmaceutical companies should work closely with regulators on the design and interpretation of these studies, and that this collaboration can make all the difference in the successful completion of studies.

Risk assessment, my little plea, can actually occur prior to approval, and the goal again is to identify subgroups of patients that should not take the drug.

Although we have several tools to carry out post-approval studies, industry is very interested in working with established thought leaders and think tanks, such as the SERTS to continue and improve the field.

Thank you.

DR. GROSS: Thank you, Dr. Dieck.

Dr. Dieck is going to have to leave momentarily. Does anyone have any questions of her? Yes, Sean.

DR. HENNESSY: As a preface, I would like to disclose that I receive grants from Pfizer although I realize that my question may change

that.

You pointed out that when drugs are marketed, there is an expectation by the public with regard to safety commensurate with them having been studied in about a million people, and I am wondering if you would like to reflect on whether the sales and marketing activities of companies contribute to that expectation, and, if so, what can be done about that both from the industry side and from the regulatory side.

DR. DIECK: I think that it is multifactorial, that expectation. I think that people have gotten a lot healthier over the past couple of generations. We don't see diphtheria and pertussis and things that people really made it very clear what the benefit of drugs were, because now we are treating things that are silent, like hypertension and hypercholesterolemia, where the risk that you would expect or accept is much less.

So, part of it is that the types of things we are treating, you would expect much less types of risk. It is hard to say, I mean

direct-to-consumer advertising has been relatively recent, and it is hard to say how much impact that would have been made on the public expectation because my assumption is that the patient is still having a conversation with their physician as to whether or not that drug is right for them.

Presumably, you know, if they had an allergy, that they wouldn't be put on drugs that could cause allergy, and so forth. I would say that I think that there are a number of reasons. I think also the cost of drugs, people think that the higher cost of drugs, they don't want to accept any risk associated with it.

I think there are many factors that go into that expectation. I hope that answered it.

DR. GROSS: Ruth Day.

DR. DAY: Dr. Dieck, Dr. Graham gave us an overview of the funding that they have for all the studies at FDA, and you have presented some wonderful studies today. Can you give us any idea about the general ballpark of costs of any of these studies or types of studies?

I know it will vary widely over time, but you have mentioned specific ones today. For example, a registry study versus something else,

just so that we can understand what the FDA can and cannot do easily relative to industry.

DR. DIECK: That is a very good question. I know that one of the registries that we provide money to, along with other companies, is 90,000 a year to the Anti-Epileptic Pregnancy Registry, so this is what we put in for that.

Normally, for some of the database studies, GPRD may be a little bit more expensive than United Healthcare, but they can run anywhere from--depending on the question--from 500,000 to a million dollars for a study.

In some instances, I think that industry is charged more. You can have smaller studies in the 3- to 500,000 range. The de novo studies are very expensive. The International Men's Health Study for 6,000 patients where we went back and surveyed physicians, and so forth, and had to set up extra sites, that was about 13 million.

The large, simple trial where we have now gone into 18 countries, and we are buying drugs, is very expensive, but we are committed to carrying out the study. I mean this is a regulatory obligation, it's a post-approval commitment, and we are doing everything we can to get the study

completed. So, a wide range.

DR. GROSS: We will take two more questions.

Stephanie Crawford.

DR. CRAWFORD: Good morning. Thank you for the presentation.

My question is pretty general, especially in terms of some of the recently highlighted events with some of the drug products. Discussions between the sponsor and the regulatory agency, of course, are very beneficial, but in terms of negotiation of how postmarketing studies will be conducted, I guess I would just like to hear a little bit about what this negotiation means.

Is it somewhat give and take, or is more directed on one side versus the other?

DR. DIECK: It can take several forms. The large, simple trial was very interesting because we were actually negotiating with both the EU and with the U.S., and there were questions about what was the appropriate comparison drug, because treatment for schizophrenia differs in Europe than it does in the U.S., we tried to find a drug that would work optimally for both regulating bodies because if we added more control groups, you

lose power, and we wanted to keep that really tight power of the minimal detectable relative risk, we wanted to keep that very small.

So, that was one thing that we talked about. We talked about the analysis like were we going to do an intent-to-treat analysis, or if patients switched to another product, we are going to do on-treatment analysis, and we decided we could do both.

The countries that we were going into, one of the challenges with this particular compound is that we thought we would get approval in a variety of different countries that we ended up not getting

approval in, and so we had to look for countries where there was an infrastructure where we could go in and do that in order to get the 18,000 patients.

Then, we had a very frank discussion at the FDA as what would we conclude if our minimum detectable relative risk was 1.5, what were we going to conclude if we had 1.4 or 1.3 or 1.6, so we had some frank discussions about that and very interesting discussions about that, too.

Remember, this is the study that had all these independent boards that are monitoring the integrity of the study. Oh, another thing with the International Men's Health Study, we couldn't complete it in time. They wanted us to complete it before re-registration of the product, and it was very clear that we were doing everything we could to increase patient enrollment, and we simply couldn't get the patients in time, so we discussed our preliminary findings with the regulators, and they agreed that we weren't tied to that re-registration.

But those are the types of conversations

that you have to have. Sometimes you just can't anticipate every problem that you are going to have doing large de novo studies, and that is why it is very important to be able to have a dialogue with the regulators to let them know it is going well and then what is not going well.

DR. GROSS: The last question is from Curt Furberg.

DR. FURBERG: I would like to commend you for your efforts and your potentially important studies.

There was a report from the IMS about the public trust of safety information coming from the pharmaceutical industry and two-thirds of the public do not trust the information they get from the pharmaceutical industry, so that is what I am asking about.

You are primarily working with regulatory agencies. I think that is insufficient. I think I would like you to work with more independent groups and get more transparency in what you are doing and somehow improve that lack of trust that the public

has right now.

So, I was wondering what are you doing, do you agree with the report that there is a trust issue and what are you doing about it?

DR. DIECK: That is an excellent question. Actually, that is something that we are very much engaged in right now is public trust particularly on the safety area.

At this point, I think that we are working well with the regulators on making sure that the study designs are of the highest integrity and that we are doing all the right things.

We are getting them peer reviewed, but you are right, we totally miss a large part of the public that is very concerned that we may not be doing anything or if we are doing something, we are hiding it.

We have been thinking about ways that we could work with--we are very much interested in the area of risk communication, and this is something that our PhRMA PVE Technical Group is very much involved with, as well, and how we can work with

advocacy groups and community groups, and even like the American College of Physicians and other groups to try and get the message out that independent people that, yes, we are doing these studies, yes, we are concerned about patient safety.

Part of what we do, the next generation of drugs, we try and make them more effective and safer at the same time, and a lot of times that message doesn't get out. If you have any ideas, I would really love to hear them, because we are scratching our head and we are really looking for ways to meet that.

Thank for you comment.

DR. GROSS: Dr. Dieck, thank you very much for your interesting and frank discussion.

The next speaker is Dr. Julie Beitz, Deputy Director, Office of Drug Evaluation Group III, of the Office of New Drugs. She will discuss postmarketing studies from their perspective.

Postmarketing Studies from OND Perspective

DR. BEITZ: Good morning. This is going to be a fairly fast overview, so fasten your seat

belts.

[Slide.]

Risk assessment occurs throughout a product's life cycle as you have heard from the identification of a potential product through the pre-approval development process and after the product is approved.

When embarking on a development program for a new product, sponsors and regulators need to consider what safety information should be generated pre-approval, in particular, what specific safety risks should be explored pre-approval, and what safety information may be reasonably delayed to postmarketing studies.

[Slide.]

Even a large development program cannot identify all the safety concerns prior to product approval. Therefore, it is expected that even for a product that is rigorously tested in the pre-market period, new safety concerns may become apparent after marketing, when the product may be used by a large number of patients chronically

including patients with comorbid illness or who are prescribed multiple concomitant medications.

Recently published guidance from FDA has stated that the size of the NDA or BLA safety database supporting a new product depends on several factors including whether the product will be used chronically or acutely, whether the product is intended to treat healthy subjects on a large scale, or a seriously ill population for whom some risk is acceptable, and whether alternative therapies are available and the relatively safety of these therapies.

[Slide.]

For products intended for acute or short-term use, or for products that treat life-threatening illness, the number of exposed subjects in the safety database depends largely on the disease indication and is typically determined on a case-by-case basis.

For products intended for chronic, long-term use, FDA guidance and ICH E1A guidance have recommended exposure in at least 1,500

subjects and multiple dose studies receiving relevant doses.

This number includes 300 to 600 subjects exposed for 6 months and 100 exposed for 1 year. More than 1,500 exposed subjects may be needed if there is a concern about late developing adverse events, if there is a need to quantify the rate of a specific low-frequency adverse event, if the product's benefits are small, or if the product may add to an already significant background rate of morbidity in the treated population.

[Slide.]

So, the fundamental challenge here is given the limitations of the pre-market safety assessment, rigorous postmarketing safety assessment is critical for characterizing a product's risk profile and for making informed decisions about risk minimization.

[Slide.]

In this presentation, I will attempt to address several topics - how are postmarketing studies regulated? What can we learn from

different types of studies?

I will highlight some of the guidance that FDA has issued to address important considerations in the design and the review of studies, and summarize some of the dilemmas we face in interpreting them, and conclude with a brief summary of the challenges that regulators face.

[Slide.]

First, the definition from our regulations. Postmarketing studies delineate additional information about the drug's risks, benefits, and optimal use. These studies could include studying different doses or schedules of administration, studying the use of the drug in other patient populations or other stages of the disease, or studying the use of the drug over a longer period of time.

When this regulation was first promulgated in 1988, it applied to drugs for life-threatening and severely debilitating illnesses, but in practice, it has been applied to any indication and covers both drugs and biological products.

[Slide.]

Postmarketing studies are required by regulation in the following three scenarios. I am

going to take some time to explain them in some detail.

The first of these is accelerated approval. FDA published the final rule in 1992 to accelerate the approval of new drugs and biological products for serious or life-threatening diseases when the product provides meaningful therapeutic benefit over existing products.

Under this rule, FDA may approve products based on surrogate endpoints that reasonably predict clinical benefit. Postmarketing studies are required to confirm clinical benefit and safety data are often collected as part of these studies.

The second example is the animal efficacy rule. This rule was published in 2002 to allow the use of animal data for evidence of a product's effectiveness to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances.

In this case, definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose individuals to such substances. Under this rule, postmarketing studies are required to confirm clinical benefit and assess safety in humans in the event an

accidental or hostile exposure to these substances occurs.

Our last scenario involves pediatric research. The Pediatric Research Equity Act was signed into law in 2003 to improve the quality of pediatric information in labeling. Pediatric studies are required for all applications involving new active ingredients, new indications, new dosage forms and dosing regimens, or new routes of administration, to assess safety and efficacy and support dosing for pediatric patients.

Pediatric studies may be deferred to the postmarketing period if the product is ready for approval in adults before pediatric studies are completed. However, pediatric studies that are deferred in this way are still mandatory.

[Slide.]

Thus, the vast majority of postmarketing studies that you are familiar with are not required by regulation and fall under one of these scenarios.

First, postmarketing studies are requested by FDA. In this case, the sponsor voluntarily commits to conducting one or more studies after approval, and a schedule for study completion is

agreed upon before the application is approved.

FDA tracks the status of these studies whether required or not. Post-quarterly updates on its website and reports summary statistics annually in the Federal Register.

In addition postmarketing studies may be requested by other regulatory authorities or may be conducted at the initiative of the sponsor, NIH, or other investigators with or without any input from FDA.

[Slide.]

A recently published FDA guidance for reviewers regarding the conduct of the clinical

safety review describes two major categories of serious adverse events.

First, there are those that are readily recognized as potential consequences of treatment. As you heard from previous speakers, these are typically hematologic, hepatic, renal, dermatologic, or pro-arrhythmic in nature.

The second category includes adverse events that are not readily attributable to treatment, because they can occur in the absence of treatment, or are known to result from the underlying disease, or are relatively common in the population being studied.

Examples that you have heard already are myocardial infarction or stroke in the elderly, immune defects in AIDS or cancer patients, sudden death in schizophrenic patients. Large controlled studies are often needed to evaluate these events either in the context of efficacy studies or in studies designed specifically to assess safety concerns.

[Slide.]

Recent FDA guidance defined a safety signal as a concern about an apparent excess of adverse events compared to what would be expected.

The guidance also states that after a safety signal is identified, it should be further assessed by conducting a careful case level review.

If the signal represents a potential safety risk, one should first develop a synthesis of all available safety information, in other words, review what is known already.

Second, one should assess the benefit-risk balance of the product for users as a whole and for at-risk populations.

Third, consider how best to investigate the signal through additional studies.

[Slide.]

In that same guidance, FDA offered the following general advice to sponsors faced with working up safety signals for their products.

Sponsors are encourage to consider all available methods to evaluate a particular safety signal and to choose the method best suited to the

particular signal and research question.

They are encouraged, of course, to communicate with FDA as their plans progress.

[Slide.]

A whole host of studies may be performed in the premarket or postmarketing period to assess safety signals including preclinical toxicological studies and a variety of clinical studies. I will discuss each of these in turn and highlight the kinds of information that each can provide.

For example, studies may provide a better understanding of mechanisms or insights regarding the magnitude, severity, and change in risk over time, or information about factors that can enhance or diminish the risk.

[Slide.]

I will begin with preclinical toxicological studies, which are generally performed before a new chemical entity may be tested in humans. During product development, a variety of types of studies are performed to predict as much as possible what potentially

serious toxicities might occur in humans.

During development or after approval, toxicities may be observed in humans that can be further assessed in preclinical studies.

We are often faced with two important dilemmas when interpreting the results of preclinical toxicological studies. Not all adverse events in humans are predicted by animal studies or are confirmed after the fact in animals.

Why is this the case?

[Slide.]

Well, there are many reasons why false positive or false negative findings could results from animal studies. Let me highlight a few.

First, very large doses that are used for some types of animal studies may saturate pharmacological, metabolic, or elimination pathways result in the production of toxic metabolites and lead to irrelevant toxicities that would not be observed in humans.

Subjective adverse events, such as dizziness or headache, are not readily detectable

in animals. Immunologic effects, such as hypersensitivity or skin reactions, are difficult to detect in animals, and rare events in humans will rarely be observed in animals as few animals are evaluated compared with human use of a product.

[Slide.]

Turning to pharmacokinetic studies, these are performed for a variety of reasons, and I have listed some here. First, to determine the optimal dosage strength, dosage form, and regimen for a product. They can also be designed to assess the extent to which factors, such as age, underlying disease, or concomitant intake of food or medications can enhance or diminish a product's absorption, distribution, metabolism, and excretion.

Also, assessment of blood or other tissue levels can sometimes assist in the monitoring of patients experiencing adverse events or overdose, and PK parameters can be used to determine the bioequivalence of new formulations relative to older ones.

Common dilemmas that we face include what is the appropriate timing of PK studies relative to product approval and what populations should be

studied. Should volunteers or patients be studies? Should younger or older patients be studied? What about patients with mild disease versus those with more severe disease?

In addition, it is not possible to assess all factors that may affect blood or tissue levels. In fact, not all factors themselves can be quantified, and in a given patient, multiple factors may be at work.

[Slide.]

A number of study design considerations can affect the interpretation of PK study results. Some of these are listed here. Was an adequate baseline for study subjects established in terms of their diet or other factors?

Was a sufficiently long crossover period built in to prevent carryover effects? Were study subjects compliant with the study-specified diet? Was a good analytical method to measure product

concentrations in metabolites available?

Were an appropriate number of blood or tissue samples collected? Was the timing of collection optimal?

Was the degree of protein binding considered? Were differences in activity of receptor binding of optical isomers and metabolites considered?

Finally, from a very practical point of view, were the dosage strengths and dosage forms studied similar to those to be marketed?

[Slide.]

When interpreting data from individual PK studies, reviewers should assess the assumptions that were used. For example, were the appropriate PK models used? Were rate-limiting steps correctly identified? Were the effects of metabolites considered, and so on?

Many PK studies will have been performed during a product's development program and even post-approval to address specific safety concerns. A synthesis of study results often needs to occur.

However, when comparing studies, it is important to consider, for example, whether the populations, study conditions, formulations, or assay methods were comparable. If not, erroneous conclusions may be drawn.

[Slide.]

Other speakers at this meeting have discussed pharmacoepidemiologic studies. Here, I will just highlight that these may be the only practical choice for evaluating uncommon or delayed adverse events.

They can help identify important co-morbidities or co-therapies as risk factors for an adverse event. They can help examine the natural history of a disease or explore drug utilization patterns.

As we have heard from other speakers, if it is determined that a pharmacoepidemiologic study is the best method for evaluating a particular signal, what is the best design to use? How large should the study be?

FDA guidance has stated that it is almost

always prudent to conduct more than one study and more than one environment and even use different designs. Agreement of the results for more than one study helps to provide reassurance that the observed results are robust.

Of course, how best to minimize bias and account for possible confounding also needs to be considered.

[Slide.]

The remainder of this presentation will focus on controlled clinical studies which can be designed to address many different goals.

In Phase II, the purpose of controlled clinical studies is to assess the effectiveness of the drug for a particular indication and determine the common short-term side effects and risks.

In Phase III, controlled studies are intended to assess safety and effectiveness needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for labeling.

However, after a product is approved,

controlled clinical studies may still provide important answers for us. For example, they can assess the safety and effectiveness of the product in populations not previously studied or studied to a limited degree.

They can help assess the safety and effectiveness of new dosing regimens or longer treatment durations.

[Slide.]

What are some common dilemmas faced when designing or interpreting controlled studies?

As you heard, controlled clinical studies are impractical when the adverse event rates of concern are less than 1 in 2,000 or 1 in 3,000. Thus, a large number of patients representing appropriate demographic subsets or risk groups must be enrolled to observe a relatively uncommon adverse event.

If inclusion criteria are set too narrowly, the enrolled population is relatively homogeneous, but study findings may not be relevant to general clinical settings involving a broader

range of patients.

Studies in Phase II and III typically do not test specified hypotheses about safety. There are exceptions, of course, when a particular safety signal has arisen in a class of products or when a specific safety advantage is being studied. In these cases, there will often be primary safety endpoints and all the features of hypothesis testing including blinding, control groups, and prespecified statistical plans.

[Slide.]

FDA regulations stipulate the content of NDA and BLA applications. Safety and related information required for clinical review include an integrated summary and analysis of safety, adverse event tables, case report forms for dropouts or patients who experienced serious adverse events, individual patient adverse event data and laboratory listings. These are usually accessible to the reviewers electronically, and narrative summaries of deaths, serious AEs, and events leading to dropout.

Other documents may include reports of specific safety analyses, coding dictionaries, and source documents for auditing purposes.

[Slide.]

Recent FDA guidance discusses how reviewers should approach the assessment of adverse events in controlled clinical studies. Assessment of drug-relatedness is fundamentally different for relatively common and relatively rare events.

For common events, one would compare adverse event rates for the product in question to that in the placebo or other control group. For rare events, the expected rate in a clinical setting would be zero, so a few cases or even a single case of a rare life-threatening event could represent a safety signal.

For events that seem drug related, the guidance goes on to suggest that additional exploration should be carried out to assess, for example, dose dependency, time to onset of the events, severity, time course of events, demographic interactions, drug-drug and

drug-disease interactions.

[Slide.]

It is important to recognize that adverse events can be over- or under-reported in controlled clinical studies. Over-reporting can occur for a variety of reasons, for example, study design issues, excessive dosing, or very frequent assessments may lead to more reported events. The study may be long enough, subset medications, illnesses or social or psychological stressors may be introduced.

Investigators may be overzealous in reporting or patients may have a heightened awareness about specific events, and improper coding of adverse events could result is less serious events being codes as more serious.

Even with an adequate number of patients enrolled, there can be under-reporting in controlled studies. Studies may be designed with in frequent or poorly time assessments relative to peak effects.

They may be monitoring inappropriate

parameters and follow-up may be too short to assess late effects, withdrawal effects, or rebound phenomenon.

Investigators might attribute an adverse event to the patient's underlying disease or some other reason. The event itself may not be recognized by investigators or patients, or the significance of an adverse event may be masked if not properly coded in the database.

[Slide.]

Controlled clinical studies give us a wealth of information about laboratory abnormalities. Typically, an analysis of central tendency comparing mean or median changes from baseline across treatment groups is performed.

Other comparisons across treatment groups focus on a number of outliers or the number of patients whose laboratory values deviate substantially from their reference range, and the number of patients who discontinue treatment for laboratory abnormalities.

In addition, the dose dependency, time to

onset, and time course of laboratory abnormalities are also assessed. Controlled clinical studies can address the product's potential for severe hepatotoxicity, and the product's effects on QT/QTc prolongation.

I would just like to mention the recent efforts at FDA and ICH have focused on the utility of conducting a thorough QT study in early product development to assess a product's effects on cardiac repolarization.

This study is accomplished by exposing human volunteers to the highest possible doses tolerable. The results of such a study are expected to have important implications for the amount of electrocardiographic data that would need to be collected in later studies.

[Slide.]

Controlled clinical studies also give us a wealth of information about special populations as defined by patient age. Some design and interpretation considerations regarding studies of neonates and young pediatric patients include:

Were doses adequately adjusted for weight?

Was the state of development of physiologic systems and metabolic pathways considered? Were potential adverse effects of the product on growth or neurocognitive development considered? Were standardized measurements incorporated into study protocols?

Was the frequency of testing, imaging, or sampling of blood or other tissues adequate given the burden these pose on young children?

Regarding geriatric patients, one should consider whether decreased renal function delayed excretion and led to product accumulation, or whether decreased muscle mass affected product distribution.

In addition, were altered hemostatic mechanisms considered?

[Slide.]

It is common in many development programs for much of the long-term exposure data to come from single arm or uncontrolled studies. Although these data can be informative, it may be preferable

to develop controlled long-term safety data, such as you heard in the last speaker's presentation.

FDA guidance describes the purpose of these studies as twofold. First, these studies allow us to assess and compare rates of adverse events for a product relative to one or more control interventions. This is particularly helpful when the event of interest is more common with cumulative exposure.

Second, these studies can facilitate accurate attribution of adverse events to the product, and this is especially helpful when the event of interest occurs relatively common in the treated patient population, or could be considered part of the disease that is being treated.

The timing of long-term controlled safety studies relative to product approval is a matter of debate. Decisions regarding sample size, study duration, and endpoints need careful consideration and can impact the adequacy of the information we glean from such studies.

[Slide.]

Lastly, a few comments about pooling safety data from multiple clinical studies. Pooling safety data can improve the precision of an

incidence estimate. Better precision is important for low frequency events.

A larger database also permits exploration of effects within subgroups, such as drug disease or drug demographic interactions. However, pooling can obscure important differences between studies. It is therefore most appropriate to pool data from studies with similar designs, for example, those evaluating similar doses, treatment durations, and study populations.

Even when the pooled analysis is the primary one, it is still important to explore the range of incidences across the studies being pooled.

[Slide.]

In summary, then, regulators face many challenges. It is not possible to identify all safety concerns prior to product approval. Studies of approved or new uses may generate safety

information that needs to be placed in context with what is already known.

That may impact the benefit-risk assessment for labeled indications, and that may need to be applied to other members of a product class or other dosage forms.

We look forward to hearing the Committee's deliberations today regarding data sources for postmarketing safety information and your advice on how best to obtain and interpret the valuable information they provide.

Thank you.

DR. GROSS: Thank you, Dr. Beitz.

We have a few minutes for some questions before the open public hearing.

Richard.

Question and Answer Period

DR. PLATT: That was a very helpful presentation.

Dr. Beitz, is it convenient for you to put up Slide No. 4? I am interested in exploring the amount of information FDA typically has about

safety at the time that drugs are approved.

As I read these data, while they are coming up, they seem to indicate that a reasonable criterion for approval is having at least 100 patients who are exposed for a year, which means that if everything goes perfectly, that is, you don't see any problems, you can't exclude a 1 in 40 chance that there is a very serious safety problem.

I would think, in my naive fashion, I would think that effectively, our policy is one of accelerated approval for all drugs with respect to safety. Therefore, I think it would be reasonable to entertain the idea of saying every drug approved under these kinds of criteria should have a postmarketing study that is designed to improve our knowledge about safety, and the size of it should be sufficient to exclude maximum risks that would depend on what the drug is and how it is supposed to be used, how many people it would be used in, but it seems to me that, not knowing what the accelerated approval authority is, that, in fact, it might be reasonable to consider the fact that

essentially every drug approved under the criteria you show there really has been approved under accelerated conditions.

DR. GROSS: I think this is an important issue and perhaps we can interact with the FDA after lunch when we have the open question period.

Right now, are there any other burning issues before we get to the open public hearing?

DR. MITCHELL: Does it need to be burning?

DR. GROSS: Yes, it needs to be burning.

Anne.

DR. TRONTELL: I see Dr. Dieck is still present and I wondered if I could ask a question in follow-up to your presentation where you were describing increased cardiovascular risks for migraineurs and patients with schizophrenia that you had done in observational studies.

I wanted to inquire if those studies, if not relative to specific product questions, measured lifestyle factors or use of nonprescription medications, dietary supplements, things that might better inform that elevated risk,

so that we could better predict how it could be minimized.

DR. DIECK: You can't see very well the footnotes there, but we were adjusted for age, gender, year of cohort entry, comorbidities in the year prior to study entry, oral contraceptive use, and estrogen replacement therapy use.

So, those were the types of things that we were able to get from the database and control for, so these are adjusted estimates.

DR. TRONTELL: That sounds very reasonable from what you might get, but other important factors, such as tobacco use, or, you know, a migraineur who is not using medication, I might presume is using some other form of nonprescription drug, and if you had any speculations or plans to study that.

DR. DIECK: That is the type of thing that probably would be best answered in a de novo study or some sort of case-control study where we would go back and, let's say, identify some of these patients and go back by questionnaire and ask them

those questions, because smoking history, as you know, is just notoriously not captured, certainly not in the United Healthcare.

With respect to the GPRD, I don't have the information at my fingertips, because that is medical records, automated medical records that we may have had more information on OTC use, at least some of it, as well as smoking use, but certainly not in the United Healthcare database.

But those are exactly some of the limitations again, which is why it is good to replicate a study in a different database, that has different variables that are available. I hope I answered that question.

DR. GROSS: Thank you very much.

I think so as not to hold up the people who came for the open public hearing, we will begin with that.

Could Speaker No. 1 come to the podium, please. You do not have a handout for her.

Open Public Hearing

Private Citizen

MS. CITRANO-CUMMISKEY: Good morning, Advisory Committee members and FDA participants. I just want to mention before I start that I did not

find any confidentiality agreement for this company, and I never received any financial gains for what I am going to say.

My name is Debra Citrano-Cummiskey and I am here today to present my story from my 23 years of experience in the pharmaceutical manufacturing business, which had a tremendous impact on the quality of all the marketed products when I was terminated.

I am going to show how my position as a lead scientist of the Corporate Reference Standard Program at the Bristol-Myers Squibb Garden City site in Long Island, New York, had affected the quality of all the marketed products released from that site and any other sites in our worldwide operation using our reference standards that I had analyzed, procured, and distributed.

To make my point, I am going to run through some overheads, so everyone can see what

happens to the quality. When this company made this acquisition with DuPont Pharmaceuticals, they were only thinking about how lucrative it would be to them, but they were careless in handling these expensive risky pharmaceuticals that they are now selling to the public.

We have all seen lately in the press the many side effects that can cause these chemicals to be pulled from the market because the risks are found to outweigh the benefits. Now we have heard all the public discourse due to the drug pricing, which causes many patients to dig deep into their pockets to pay for these drugs that they are forced to buy.

Now, what about the quality? I just want to quickly show you a list of some of the compounds I was responsible for handling and distribution to our Garden City site and worldwide licenses, as well as all of Endo Pharmaceuticals and Merck's Cozaar and Hyzaar.

You can just flip to the next view. It is just some compounds that we had, I was responsible

for, private list.

Here, I have a copy of my promotion, which I received in March 2001 for handling all of my responsibilities so well, and I was very proud to accept, and you can see I was promoted to a Lead Scientist.

By September 2001, it became known that Bristol-Myers Squibb was going to acquire the whole DuPont Pharmaceuticals business. Although the employees thought this would be great to be working for Bristol-Myers Squibb since they had such a good reputation, but in this acquisition, they were not what they seemed.

We had a very large calculation error that I described in detail in my letter to Dr. Lester Crawford, which occurred in the Raw Materials Laboratory that was also just discovered. This error was something that the management at DuPont Pharmaceuticals thought it was better not to tell their new owners since it was so embarrassing and so many of these products were affected.

They feverishly turned the laboratory

upside-down, searching for ways to cover this up. Everyone's notebook was taken from them, so the management can find a good excuse or a scapegoat, so they would look as though they were doing their job as managers.

Unfortunately, this was the first look at notebooks by management as they were usually too busy to bother with notebook checks.

Here, I have a handwritten note I had placed on m notebooks, describing the time period of the error. Let me also describe the magnification of this error by starting in the raw materials and reference standard potencies issues and release, in some cases, with a 5 percent error in purity.

In one case, hydromorphone HCL raw materials actually failed the release limits, which was also released as a reference standard. This failed raw material went into the finished product and this same lot issued as a reference standard was used to test the hydromorphone hcl finished product tablet.

This error had compounded into a cascading error that is becoming very difficult to hide. On October 1st, which was the close of the

Bristol-Myers sale, the lab became extremely tense as the FDA was also coming to the Garden City sit for a pre-approval inspection for some of Endo's ANDAs.

The management came up with the quick idea of sweeping this whole mess under the reference standards as it was uncommon to place the blame here to save a failing batch of finished products.

I would ask my management on the way to the meetings why I get called into every meeting whenever a finished product was failing, and their response to me would be, let's just blame it on the reference standards since it will be the easiest number to change.

My guess is this is exactly the way they handled this very serious error, because I was sent home on administrative leave on October 8th, so I went to New York State Division of Human Rights to find out why my rights were so violated when

everyone else who took part in creating this error only received a warning.

By February 1st, 2002, I received a letter of termination via Federal Express. You can see my letter of termination says I didn't follow SOPs, which is fraud in our business, as we all know.

The letters I have distributed describe how I tried to get answers, but this is when I was told I did nothing but fraud in my 10 years as a Corporate Reference Standard Coordinator.

Now, I am wondering why I was allowed to stay in this position, and none of my management was aware of what I was doing, but still promoted me to a Lead Scientist of reference materials. How come they always brought the FDA to me on every GMP inspection, audit, and pre-approval inspection, and I was never written up in any 483, as many of my fellow chemists were?

How can they call all my work fraud to the Bristol-Myers attorney on their defense when they signed off on it and wouldn't have if I wasn't doing whatever they told me to do?

This is how I am showing that the quality of everything ever released against my work had more than just the titration error problem

incorporated into their products. I also attach the letter I had written to the CEO of Bristol-Myers Squibb while I was in court, showing how they were making an even bigger mistake by terminating me for fraud, as it affected all their product quality even more than the titration error did alone.

When I read the article in Newsday, dated March 31st, 2005, written by Delthia Ricks, on Coumadin, showing the death rate of the patients on Coumadin died more frequently than the patients just taking aspirin, I wondered if the product quality of Coumadin was attributing to the riskiness of this drug study.

I decided I was not going to present this data I have to show other companies do this, as well, to save expensive raw materials from being thrown out when batches fail, so they can still ship their product.

This is a company I worked for while I was court with Bristol-Myers Squibb, but I am going to reveal the product was a contract this company had, and not the company name since I did not officially inform the FDA on this company for fear of the same outcome I had already experienced.

This data would have shown that the vitamin had been released at two times the level of the release limit for this product. The company releasing this product had many GMP violations and I resigned right after I saw this happened.

My resignation may have been triggered because I blew the whistle before and I didn't want to see any more of this. Maybe I can just move on with my life now, now that I have told the right organization, the FDA, who can determine whether or not these companies are right or wrong when not following GMPs.

We are talking about expensive risky drugs, and we are not talking about candy.

In closing, I would like to quote Thomas A. Kempis. "He who does not shun small falls,

falls little by little into greater falls."

Thank you.

DR. GROSS: Thank you.

I neglected to read a statement before we began this, so I will read it now.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The next speaker at the open public hearing is Speaker No. 2, and you have a handout with green and gray letters from them.

Quintiles Strategic Research Services

DR. STEPHENSON: Thank you, ladies and gentlemen, for the opportunity to speak today.

For those of you that want to know me as more than Speaker No. 2, my name is Hugo Stephenson. I am a physician and I am the President of Strategic Research Services at Quintiles Trans-National, which is one of the largest providers of research services to the pharmaceutical industry.

From the perspective of financial disclosure, I am very, very involved in this

process.

I am actually responsible for all Phase III-B and IV activities within Quintiles globally. That includes active surveillance, and I am actually here today to really discuss some practical recommendations for the FDA, really representing the arms and legs that do this research to dramatically increase the amount of prospective research actually being conducted by industry primarily, but industry and government here in the United States.

Now, we have heard earlier today from David Graham about the limitations of retrospective research, the cost of databases, and appropriateness of data. We have heard from Dr. Beitz, as well, about really the preferential robustness of prospective studies, whether they are large randomized trials or whether they are large, simple observational studies.

So, the question that I would really like to discuss today is what can the FDA do to facilitate more prospective research here in the

United States, what can be done, so we can actually move on and have more data.

I am going to flip through a few slides. Obviously, I have changed what I was going to say a little bit on the basis of the discussion that has already existed around retrospective data.

But I would really like to look at what the obstacles are to prospective research, and I am saying this as a company that is doing the trials on behalf of many of these pharmaceutical companies and also on behalf of governments around the world, what do we experience.

First and foremost, we see really low physician motivation to participate in these studies. What does that mean when I go out and I say, "I have a postmarketing surveillance study, Doctor, do you want to participate in that?" Less than 20 percent of doctors even respond. That's not respond yes or no, that's even respond to the request, and of that 20 percent of doctors that respond to the request, we find that less than 50 percent of doctors that respond actually enroll any

patients or enter any data in the system.

The second thing that we see is low presentation of patient benefit. Most of the patients that we deal with in the postmarketing environment assume the drug has been approved and therefore it is safe. They don't recognize the value of participating in a postmarketing study as actually a way for them to experience a risk management program and the way to actually engage in better patient protection.

We see that the fragmented pharmacy and reimbursement environment here in the United States makes it much more difficult to actually perform large population-based research activities, and I will give the UK as an example.

Pharmacies around the United Kingdom actually send the prescriptions to a central clearinghouse for reimbursement. It is possible in the United Kingdom, in fact, it has been used a lot, for that central clearinghouse to send out a green card to physicians six months after prescription has actually occurred to follow up

from the patient what has actually happened.

Now, what is the significance of that? It means that we are not burdening physicians with the administrative workload of running these programs when we get much better compliance. We see that there is a haphazard IRB environment here. Again, I will summarize the experiences that we have.

We will take a large, simple study. We are going to go to one central IRB to cover maybe 50 sites, and we are going to go to another 20 IRBs to cover another 20 sites. The administrative overhead associated with a simple questionnaire can be quite significant, and it can be quite a burden for hospitals and physicians wanting to participate in these studies.

Now, I use France as a comparator here where I can actually go to one IRB and then I have got mutual recognition of what is being performed. So, I can actually say I want to start a postmarketing surveillance study, I am going to go out there, get one approval, and start the study tomorrow rather than looking at three- or six-month

delays that we experience here in the United States.

There is also inconsistent IRB decisionmaking, and I use informed consent as a good example. I have an example from just last week, where we had a simple surveillance protocol that involved no treatment intervention to the patient, it was just follow-up, that involved no mandated visits, involved no mandated investigations.

Three IRBs came back saying that they would allow waiver of informed consent, and therefore much more straightforward data collection. Six of them came back saying that they actually would not waive informed consent.

So, we are looking at this kind of variation just within one study.

Now, the next thing which we look at is confusion regarding adverse event safety and monitoring processes, and in many ways I think I can speak for a lot of our sponsors that want to conduct studies, but are really unsure of what

level of monitoring is really required for these studies.

For those of you that aren't aware, in a Phase II or III study, where the drug isn't approved, we will go out to doctor sites six weekly, 10 weekly to check the data has been entered correctly, and so forth. Why? Because we are there to be not only managing data quality, but managing patient risk.

Once a product is actually approved, once a physician is actually prescribing within label, is it necessary to be completing that kind of activity? We see so much confusion. Studies that could be $400,000 or $100,000 in cost end up totaling 9- or $10 million just on the basis of many of these administrative processes that add very little value to the actual scientific question being addressed.

Last, but not least, we see a large amount of HMO and doctor swapping and attrition rates that affect our research.

Essentially, in bringing this to a close,

I would really like to talk about the recommendations that I have got. Primarily, we have heard over a day and a half that facilitating more post-approval prospective research is the only way to definitively improve drug safety without compromising patient access to treatment.

We have got the retrospective databases, but that shouldn't be an excuse for us not to be doing the gold standard research and facilitating it as much as possible.

So, what can the FDA do? We can increase the investigator motivation for participation, so we can negotiate with sponsors published risk management and surveillance plans like are now being proposed in Europe, so as a condition of approval, the pharmaceutical company has a risk management program that they offer as part of the marketing approval.

Second of all, a label warning for prescribing physicians to make them and patients aware of the fact that a risk management program exists. Now, if a doctor knows that a risk

management program exists, it is on the label. It's at their peril that they would prescribe a patient on a product without involving them in this kind or program.

So, we are increasing the motivation of physicians, but we are also presenting this as a benefit to patients. It is for improved patient protection.

The second thing which we can do is decrease administrative workload. So, look at the concept of what we need to do to have single central IRB approval for observational safety research. For observational safety research, how can we make it shorter rather than six months to start-up, all of these sites and millions of dollars in administrative costs, how can we make it so simple that we just give it to a doctor and say, "Hey, Doctor, here is the study, you can start participating on day one."

The second one, which is an important one, is an FDA statement through informed consent monitoring and safety reporting guidelines. The

industry is not going to put up its hand and interpret GCP in this environment when the FDA has not made a statement here.

So, what is important for the FDA around informed consent? Is it important to have informed consent if we are collecting data from patients that meets HIPAA guidelines, that doesn't involve any treatment mandate, that is purely looking over the doctor's shoulder, no investigations, no tests?

What monitoring does the FDA really require for these kinds of studies, and what are acceptable practices?

Lastly, from a safety reporting perspective, what are the obligations on the sponsor for collection and management of serious adverse events and presentation to the FDA?

They are very, very simple responses, and I know they are not talking at a level of legislation, and so on, but we deal with that every day. Implementing these could reduce the cost of studies significantly and make it a lot easier for physicians and patients to participate.

So, on that note, thank you very much. If there are any other questions, I am happy to answer them.

DR. GROSS: Thank you, Dr. Stephenson.

The next presentation is from Speaker No. 3.

DATATRAK International, Inc.

DR. GREEN: Good morning, everyone. My name is Dr. Jeff Green. I am President and CEO of a publicly traded company named DATATRAK International, which focuses on the electronic collection of clinical trial information.

I would like to leave you today, when I get done with my short 15 minutes, with something to think about, and the question I would like you to think about is: How do you react to what you don't know?

This question is posed. Are we doing our best in 2005 to fulfill the ethical commitments to patients by waiting to collate information in clinical trials on paper?

I will give you the punch line at the

beginning, and then I will substantiate it with case information and evidence. My answer to that question is no.

My previous experience, I spent 10 years as a clinical trial investigator at Case Western Reserve University School of Medicine. I participated in over 90 clinical trials and have talked hundreds of patients into being in clinical trial projects.

I have lived with three-ring binders of paper and the yellow sticky toxicity.

Patient safety in clinical trials is paramount. Isn't it being handled correctly right now? In my opinion and my answer to that is no.

Ninety percent of trials use paper, which have an insurmountable built-in four- to six-month delay in order for data to be available in an analyzable format, because it is picked up by hand and double-punched into a database in 2005.

What you don't know you can't react to. Someone may say, well, isn't the 24-hour call requirement by principal investigators an

appropriate protection? The answer to that is no, for two reasons.

The individual principal investigator has no access to a cumulative database. They are only responsible for their 10 to 20 patients that they see at their particular site. They have no responsibility for the perhaps 4,000 patients that are being enrolled worldwide, so there is no judgment that can be made on that. It is not their responsibility anyway, it is the responsibility of the sponsor.

Secondly, most adverse events that have required drug withdrawal have been adverse events that are not 24-hour call-ins, but fly in under the radar screen, such as liver toxicity with Oraflex and Selecrin [ph], such as cardiac valvular problems with fen-fen, such as cardiac abnormalities and events with the Cox inhibitors, such as stroke incidence with the NIH project looking at estrogen therapy in women to order to prevent hip fractures.

With electronic data capture, you can

delay, but you can't hide. With electronic data capture, you have audit trails of every log-in and every entry into a database to see who has accessed it, when they accessed it, and how long they accessed it.

What you don't know, you can't react to, and if you don't look for weeks to months, it is impossible to know. I am going to show you some evidence in the next slide.

If no one raises the bar of performance, everyone is therefore compliant, and there is no advancement on a new standard of practice.

The Cox inhibitor issue has really two situations, and it is either one answer or the other. Either the manufacturer knew about problems before, and they didn't react, and that is being handled by a different office, or they had a failure to know, and if they had a failure to know, if they were running the clinical trial in paper, there is an automatic delay of 6 to 9 months before you have that information in the digitized database in order to make a judgment.

This is a project that we are currently running at this time. It is enrolling 7,000 patients at 350 sites in 15 countries. What you

have on the y axis is the days between the data entry by the investigative staff and when someone logged in to review the information from the monitoring perspective, whether it's a CRO, mostly in this case, of the drug sponsor.

Each of these lines represent the countries that it is being run in. Thankfully, the red line is the United States where they took a while to get used to it, but later on, after they got used to using the system instead of paper, within 10 days, 10 to 20 days, they are logging in to review the information.

But that is not true at some of these countries that waited as long as 80 to 180 days after the information was entered by the investigative staff before it was even reviewed. This is just review. It will now take two to three at earliest to get the information entered into a database where it can be analyzed in a statistical

format to make a judgment whether or not there is any adverse events flying under the radar screen. You can't react to what you don't know, and if you don't look, it is impossible to know.

There are other examples. I apologize for the detail of the slide, but this represents 11 clinical trial projects ongoing at this time. In the far lefthand column of the totals, this represents 1,200 investigative sites, 3,300 users, 340 CRAs, 16,000 patients, and 2.8 million data entries all tracked automatically via audit trail.

The excuse we get from many pharmaceutical companies is physicians don't want to use computers. I find that hard to believe that after 12 years of post-high school education, these educated individuals are intimidated by a machine, which I have never bought.

Here is data that shows that is not true. When we looked at the date of the patient visit to the date of entry, most of the physicians in investigative sites entered the data within 10 days of the visit, so they were complying very

appropriately with entering the information in an electronic format. That is because the sponsor built into the contract they should enter the data within 5 days, and having been an investigator, if you will compensate them appropriately and faster, they will push the button on Friday, and they will send the information to you.

But this value proposition was destroyed when you look at the data entry interval to the query period by the monitoring staff, and the monitoring staff waited 3 months on average before they even reviewed the data.

Then, you look at when the query was raised, how long did it take the investigators to react to the question, you see a different time frame than the first one, and it is a little bit more delayed going out into 40 to 45 days.

The answer there is if the investigator saw that it took you 3 months to respond to my information, it is obviously of no urgency to you, so why should I hurry.

What are other examples that we can point

to? Well, there is a patient care example. If any of us would go to the clinic this afternoon because we had the complaint of being tired, and the physician drew a blood sample on us and waited 3 months for the paper to work its way through the system, and that blood sample happened to show leukemia, they would be sued for taking 3 months to take action to information that took so long.

But yet in the clinical research environment, when you utilize paper, you are waiting 6 to 9 months as evidenced by this data here, actual trials, before you are reviewing it. I think investigational data is a little bit more risky than a routine blood example.

EKG parallel. The Cardiovascular Renal Advisory Panel Committee several years ago appropriately recommended for the prolongation of QT problems with antihistamine and other drugs that digitized electrocardiograms be deployed in these trials because they are more accurate than paper electrocardiograms.

So, there is a precedent that already

exists to look at the most accurate information possible, and if you have ever looked at handwritten case report forms, which is why they double enter them hoping that two people will enter the same value that they thought a physician wrote down, you realize that digitized information, by definition, is also more accurate than paper information.

There is a precedent on the investor side. The Securities and Exchange Commission several years ago implemented EDGAR, and EDGAR is a process where all information from public companies, instead of sending boxes of annual reports and 10 K's and 10 Q's, that is all posted electronically, and minutes after a button is pushed at all public companies, the investment information is available to investors for review.

Another branch of the Federal Government has instituted a process which is electronic, which is expeditious, which is probably less costly, and which provides information faster.

The pharmaceutical industry ties into,

through IMS Health, pharmacies routinely and sucks out prescription use information down to the zip code in order to compensate their field sales force. Apparently, adoption of technology has not been a problem for that objective.

There is a disturbing lack or urgency for timely data awareness in clinical trials that would never be tolerated in the example above. One would logically think with the uncertainties of administering investigational agents that the ethical urgency would actually be greater.

EDC is a disruptive technology, it moves people's cheese, and it is hard for people to change their behavior, and that is true for all of us. However, the real problem where I have to draw the line as a professional and as a person is when that excuse not to utilize something more advanced has the chance to potentially harm someone else, that's a problem.

Patients would find the realities of data processing and clinical trials, in my opinion, rather surprising. I have enrolled hundreds of

patients in clinical trials, I have talked to spouses and subjects going in clinical trials that it is okay for us to put a catheter in your ventricle, so that we can measure cardiac output, and it would be nice to know that the people behind you are watching signals of adverse events or lack of efficacy of a drug, and that as soon as they know those signals, very appropriately, they are making a phone call saying hold off on enrollment until we find out what is going on here, when, in reality, the information is buried in stacks of paper for 9 months.

There is suggestions that this can be handled appropriately today, this technology is available today. In my opinion, and suggestion, the FDA should take a lead role in raising the bar and increasing the standard of practice expectations in clinical trials for data awareness.

It is even available in an automated, statistically valid format. Through linkages with SAS, one is able to get worldwide EDC data from hundreds to thousands of locations around the

world, automatically placed into a warehouse or repository, which is SAS drug development, and be able to have analyzable SAS data sets update automatically every 24 hours, which completely eliminates the Fed Ex process, the double punching of data into traditional CDMS systems, the manual extraction, transfer, and loading process from statisticians, and is able to give you your information updated every day.

Thank you for your time.

DR. GROSS: Thank you, Dr. Green.

There is one other speaker, Speaker No. 4.

Public Health Resources, LLC

DR. GREBERMAN: Thank you very much. I very much appreciate the opportunity to speak to this group and compliment, I believe, some of the comments that have already been made, and suggest some areas that some of the issues that have been raised could be addressed.

I don't have any slides. I fortunately was given permission to talk yesterday, but I very much appreciate being part of this team.

Basically, my name is Melvyn Greberman. I am a physician, Director of Public Health Resources, a company that provides consultation to

government agencies and industry in the public health and clinical sciences. Examples include health informatics, research design, pharmacoepidemiology, suggestions for interagency and public and private sector collaboration and regulatory affairs among other issues.

Basically, I think it is also important to indicate that I retired from the Public Health Service most recently with the Food Drug Administration a few years ago where my most recent position was as Associate Director for Medical Affairs in CDRH's Division that is now called Division of Small Manufacturers International and Consumer Assistance.

My principal role, however, really was as representative of the Commissioner's Office and principal FDA Representative as a whole to the HHS Data Council, National Committee on Vital and Health Statistics, and a number of other

interagency and public/private sector collaborative activities that I will bring into the discussion that we have shortly.

Basically, with obvious reason, much of the discussion has focused on drugs with some indication of biologics and alternative therapies. However, I think it is also very important to consider devices in the discussion here, and approaches that we would take in defining data and how to look at the data in considering both drugs and devices together.

Clearly, there are combination products and clearly, many, many health problems are treated with both drugs and devices. I am sure we can come up with many examples in cancer, heart disease, seizure disorders, among others, that we can talk about, but clearly, it is not one or the other that this group has to consider. We really need to consider the context and various approaches that could be taken in looking at the data and how to consider it.

Basically, I don't mean to minimize the

difficulty in linking to databases. I know when I was with the Agency a couple of years ago, there were great difficulties in getting the adverse event data both from CDER and from Devices to be able to be linked together.

Perhaps somebody in the room can talk about that now, and I am sure there still exists considerable concerns about how to do that effectively, but I think it is something that must be addressed.

Also, I think it is very important to address the issue of how to collaborate and share data, as we discussed, with other communities, both in the public and private sectors. I will have some suggestions for that along the course of my discussions, too.

Basically, based on my experience, there was a great deal of these discussions in terms of sharing data, how to coordinate the systems effectively at the National Committee on Vital and Health Statistics and the HHS Data Council, and in other forums where we had the opportunity to share

with people who had an influence in their various agencies to come up with solutions to these problems, and in many cases, were able to come up with solutions.

After I retired from the FDA, I know Randy Levin took over as representative to the HHS Data Council, but I think it is important to look at some of the other groups, too, in terms of how some of these problems can be solved.

Clearly, there are many links with the standards community that were in place then and still take place, that also provide real opportunities for talking with people who could influence the way their agencies dealt with these situations, so there could be more effective collaboration.

As examples, we have talked about the VA, the speakers have talked about the VA and CMS collaboration, but I think there are also some real opportunities for collaboration with the Department of Defense.

We had some good track record with that

several years ago. I know I have talked to the DoD folks, too, and they are very much interested in exploring opportunities for collaboration with FDA, so I think that is something that also could be explored, just as you are dealing with the VA now and CMS.

There are some very specific people to suggest in some of the other agencies that cut across lines, that can help in interagency collaboration. For example, there has been some discussion. Somebody brought up the SERTS' activities. The Agency for Healthcare Research and Quality is clearly interested in several of the standards activities, certainly patient safety issues, and Mike Fitzmorris has been a very good person to talk to in terms of some of the interagency collaborations that could be potential.

Another person with whom I have had some experience several years ago was Jim Scanlon in the Office of the Assistant Secretary for Planning and Evaluation, and Jim would be a very good source with his activities on NCVHS and the Data Council.

There has been some concerns about standards of practice just raised in the last talk, and some discussion regarding the Joint Commission

on Accreditation of Healthcare Organizations, discussion with Margaret Van Amerage [ph], Vice President for External Relations. She has the Washington office, would be very supportive, I am sure, of looking at how FDA and JCAHO could work more effectively together in solving some of these issues that have been raised.

Clearly, a number of professional organizations have been talked about. I could increase the list, I am sure, I am sure we all could, but I know there have been a number of discussions. FDA has participated in activities of the Drug Information Association and the Food and Drug Institute, and they can provide also for some discussions related to some of these issues.

One other group that I think is worth thinking about, given some of the discussions we have had today, clearly, the National Coordinator for Health Information Technology, David Brailor.

I have had some discussions with him in the past and clearly, he is very much interested in pharmaceutical issues.

We have talked about data sharing, we have talked about electronic health records. That is where a lot of the action is taking place now. So, I think having them understand the scenarios, the issues that need to be discussed and resolved would be a very good opportunity for looking at support at a higher level in terms of dealing with some of the real world issues that we have to face.

I think that will be enough for discussion now. Perhaps we can talk a little bit later, too, if you have any questions, I look forward to that.

Thank you.

DR. GROSS: Thank you, Dr. Greberman.

Is there anyone else in the audience who would like to make a comment at the open public hearing? Yes.

Audience

DR. JULIE: Could I have one quick comment?

My name is Dr. Neil Julie. I am a hepatologist and a clinician, and I wrote one of the first papers on troglitazone hepatotoxity. I

just wanted to address the question briefly of assessing delayed toxicity to this committee.

I would like to discuss that in the context of Med Watch monitoring. In a situation where a drug is taken off the market, the only not-for-profit remaining efficient means to monitor the cohort long term, I think is probably longitudinal follow-up of Med Watch's, with their reported adverse events.

Even though we know that Med Watches do not determine causation, it is a treasure trough of data. My question for the Committee is this. Shouldn't you or some agency track this data, follow these patients, and report their long-term outcomes after a drug is off the market?

DR. GROSS: Paul or Anne, you want to answer that, or Mark?

DR. AVIGAN: I think there is a short answer and then there might be a longer answer.

Just a short answer is that with Med Watch forms and with our AERS analysis that we talked about yesterday, we do do, with cases of interest, as was alluded to, to follow-up, and we are very interested in long-term clinical consequences and other consequences of adverse events when they do occur, so I would be very much in agreement with the concept that we are not just trying to get a narrow snapshot of an event without clinically contextualizing these events.

But I will speak with the speaker to find out more about what he was getting at, and I am in agreement with the idea that we want to know about long-term consequences of such adverse events when they do occur even if they are rare events.

DR. GROSS: Thank you, Mark.

Are there any questions from the Advisory Committee members for any of the speakers during open public hearing?

[No response.]

DR. GROSS: At this point, I would like to turn to Dr. Paul Seligman, who has an announcement

and a comment.

DR. SELIGMAN: Thank you, Dr. Gross. I do have an announcement and comment.

As you know, members of the Advisory Committee take valuable time from their personal, as well as professional lives, to provide advice to the FDA on some of the most challenging and difficult and sometimes controversial public health issues facing the FDA.

The privilege for serving on an Advisory Committee, however, is time and term limited, and on occasion we do come to a point in time when one of our members has indeed reached the limit of their service.

We have such a person in our presence today who is a charter member of the DSaRM Committee, Dr. Ruth Day from Duke University. Ruth has distinguished herself on this committee, not only because of her almost perfect attendance during her tenure on this committee, but also I think because of the extraordinarily valuable contribution she has made by lending her expertise

in the area of medical cognition, labeling, research methodologies, and the important aspect of behavior in not only the way the risks of drugs are managed, as well as the way they are in particular communicated.

I know I think I can speak for the members of the Committee, I can certainly speak for myself, that you have added a tremendous value to this committee and have not only served as a source of great information, but has taught me a lot about the importance and value of behavior of cognition and all that we do in the world of drug safety.

For the privilege of having served on this committee, I understand you have willingly accepted the role of a special government employee in the future, which will allow us to continue to tap into your expertise, and for that we thank you.

But you will also be receiving via Federal Express a certificate suitable for framing that recognizes your contribution to this committee, as well as a plaque that is suitable for, well, I am not quite sure.

But, Ruth, please, from the bottom of my heart, as well as from the rest of the committee, thank you again for your service on this committee.

[Applause.]

DR. DAY: Thank you very much, Paul. I would just like to say it has been a privilege to serve with so many bright, dedicated, and caring people, both on the committee and at the FDA.

Thank you.

DR. GROSS: I would like to echo Paul's comments, and we really appreciate your contributions to the committee, Ruth.

With that note, we will take a break for lunch and reconvene at 1 o'clock.

[Whereupon, at 11:58 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

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A F T E R N O O N P R O C E E D I N G S

[1:10 p.m.]

Questions to the Committee

DR. GROSS: You all are familiar with the questions from Day 1. Shalini asked if you have any comments on those to please feel free to sprinkle them in with your comment on the Day 2 questions.

Let's take them one at a time. You have all read them, so I am not going to read them all. I will just start with No. 1.

Under what circumstances are each of the following types of studies best suited to detect or quantitate a risk in the postmarketing setting:

Epidemiologic studies, clinical trials, registries.

DR. MITCHELL: Is it out of order to just pose a few questions left over from the morning session, that would help clarify at least for me?

DR. GROSS: It is not out of order if we all don't do it, but since you asked first, you will ask for everybody. Go ahead.

DR. MITCHELL: There is two basic questions, both directed towards the Agency and whoever feels it appropriate to answer. One has to

do with the way the Agency, and particularly the Office of Drug Safety, views their obligations and opportunities with respect to drug safety studies, both in terms of their relationship with the industry-generated studies, because clearly there is an interest within the Agency to have available to it data sets that allow it to do its own exploration.

So, there may be a legal, may be a philosophic issue there, and at the same time, in a way the reverse is how much does the Agency feel the need to evaluate data that it has under its own control through contracts or whatever versus collaborative arrangements with other organizations, academic or otherwise, that may have data that could be provided, raising issues of control and primary analysis, and that sort of thing.

So, that was one question. A sort of

related question is that there is a frequent reference to population-based studies, particularly in the questions that we have been asked to speak to today, and I would like, for one, to get a little more clarity about whether that term is designed to be restrictive to something that is strictly a population-based study, or is it also designed to include things, such as cohorts, like the pregnancy registries, case-control studies, other data sets that may speak to issues of drug safety.

DR. TRONTELL: People seem to be looking at me expectantly. I am not entirely sure of the drift of your first question, so let me take a stab at what I think our general approach is.

I think the Agency approaches any data that comes to it with sort of a healthy skepticism, that we ourselves enjoy the opportunity and believe we add value and scientific rigor by being able to do our own independent analyses of the data.

But in some of the things you have heard discussed over the last several days, we have been

using data sets in some instances collaboratively, in some cases on our own. I don't think in any way that we would want to discourage collaboration, but I am not sure if there was a message behind your question. I will let you clarify.

DR. MITCHELL: You know I am not subtle. No, I think that you have answered it to a large extent already, but I think it is a question of whether the Agency doesn't see a role for studies that might be conducted by organizations like pregnancy registries, for example, in terms of contracting with an independent or academic-based organization to have some kind of access to those data, but not have them in-house, available for the kinds of analyses that you have just described.

DR. TRONTELL: I think realistically, we don't believe that all these data, for a variety of reasons, would be able to be made directly available to the Agency. So, I think our desire is to see as much of the data as possible to give us insights to its analysis and interpretation, but I can't state any broad policy at this point.

DR. MITCHELL: The other side in terms of the way you see FDA's role in looking at data versus industry's role, I mean clearly there are

situations where FDA might look at studies or potential issues in databases that industry may not have looked at.

I mean is that based on an internal decision within the Agency that there is an issue that requires pursuit, that has not been pursued, and where does it become industry's responsibility, where does it become the Agency's?

DR. TRONTELL: I think that is a more complex question and probably is going to be best answered in the specific. As has been described, the Agency's ability to require studies, postmarketing is somewhat limited. It is constrained usually to instances where they are passing on the approval decision of a drug product where we have greater ability to speak persuasively to their needs.

The strategic design of whether FDA or industry both do a study or one does a study rather

than the other, I think we would be interested in hearing the Committee's opinion on that.

DR. GROSS: Dr. Stemhagen.

DR. STEMHAGEN: Actually, that was a very similar question that I had from the industry perspective in terms of the question of informing industry, so there is transparency if the FDA is doing studies, because I know there have been instances where companies are going to certain outside databases to do a study and have been told, oh, the FDA is already doing a study there, and there doesn't seem to be always the transparency in terms of what kinds of activities are going on and how that works actually and how that might be improved.

I guess there are certain specific instances, both in competing studies, so that the industry isn't doing the same study, if the FDA is already doing it, they would perhaps do it in some other database or whatever.

The other is if you do studies and you find negative results, that is very important

information, as well, and if we have to wait until it is published, which could be a year later, that isn't so helpful.

So, it is really the question of how that communication can be facilitated.

DR. TRONTELL: I take your question really almost more as a comment. I think the Agency has done a number of things in the last year to be more explicitly transparent in it activities, and I think certainly looking at our processes for conducting these studies, you know, should have similar questions of transparency raised.

I think if it's an issue of competing resources or trying to allocate studies of a particular drug safety problem in perhaps different populations, so you have some of the complementarity that Dr. Dieck talked about this morning, I think would all be the desired outcomes of that.

The issue of FDA doing studies and finding negative results is also one I think that is interesting for us to consider as part of a process

standpoint, you know, that it is really a piece of valuable learning information that we might be able to share with others.

DR. STEMHAGEN: That would be great.

DR. TRONTELL: I think Dr. Mitchell had a question about what we consider a population-based study, and I will look to my colleagues from FDA if they want to give additions to this, but I think when we speak to population studies, again, we are speaking largely in contrast to our spontaneous reporting system where the exposed population is uncharacterized, you know, a registry that captures a defined population in some systematic way where we might presume there is representativeness, then, I think that might well pass.

DR. GROSS: Sean has a literal answer, he promised, to Question No. 1.

DR. HENNESSY: I will reinterpret Question 1a from epidemiologic study to observational study since, as an epidemiologist, I consider clinical trials to be epidemiologic studies, as well.

I will reinterpret clinical trial to

include large, simplified trials, and I will reinterpret studies of registries as being epidemiologic studies.

So, given that reinterpretation of the question, we would want to do an observational epidemiologic study when a randomized trial is infeasible or too expensive. We would want to do a clinical trial when they are logistically and fiscally feasible.

A study in a registry is an epidemiologic study. It's an observational since we are watching, and not feeling an intervention.

DR. GROSS: You do a registry?

DR. HENNESSY: I would lump registry in with observational studies, so they are done when it is infeasible either logistically or fiscally to randomize.

DR. GROSS: Anyone else have anything to add? Yes, Curt.

DR. FURBERG: I agree with that definition. I would like to just expand on the clinical trial issue. I don't think we have taken

full advantage of the clinical trials to answer questions about the adverse effects, drug safety. Most of them are focused on efficacy, and we have a tremendous mismatch, and the experience with the Cox-2's is a good illustration where the trials that led to approval focused on one group of individuals, very different from the patients that ended up getting the drug, so it's a tremendous mismatch between the patients that get into trials and those that eventually end up taking it.

That is how we are missing a lot of important information, so the plea is for the FDA to get more involved in the pre-approval trials to make sure that the proper questions are asked about drug safety, and that information is collected.

DR. TRONTELL: Dr. Furberg, can I ask you to elaborate, because Dr. Beitz talked quite a bit about the pre-approval safety efforts, and that is often quite an extensive dialogue between FDA and the industry.

Do you have specific recommendations?

DR. FURBERG: No, but I am sure I could

come up with that if you gave me a little bit of time, the mismatch is what has made me reflect a little bit more on it, and protocols are typically developed by industry and the purpose is to get the drugs through approval, and as I said, with emphasis on efficacy.

We need someone representing safety to be involved in the review of the protocol, to be sure the right questions are asked, the right hypotheses. You collect information, you look at the bigger picture of safety rather than collecting information on 200 different side effects when they probably can be combined, and you can learn much, much more, and do it in a strict scientific way.

DR. GROSS: Question No. 2. In light of the time and effort entailed in conducting population-based studies: (a), what kinds of safety problems are best studied by these methods?

Dr. DalPan covered this quite well during the morning session. Does anybody want to add anything?

DR. GARDNER: I am afraid I don't

understand the questions. It is not the questions per se, but the reason for the questions. Questions 1, 2, and 3 have been amply covered by the staff coming in our direction for the last two days, and they really are pretty much epi-textbook, and I feel like we are doing a quiz, so I would rather know exactly what the Agency--why they phrased them in this way, what were they hoping that we would do with these questions, what do you really want us to do, not give you the answers as they appear here?

DR. TRONTELL: We have put before you what we think is our best thinking of how these data resources might be used. If you have additional thoughts, specific examples, specific limitations or strengths that we haven't mentioned, we would certainly appreciate those.

I think in Question 2(b), I think we are asking something a little outside the strengths and limitations of the data systems that we have discussed, and draws a bit upon some of the remarks that Dr. Graham made this morning about how you

might set priorities in a world where resources are not infinite, to approach these studies in population databases are typically more expensive and more lengthy to conduct, so we would appreciate your thinking on that.

DR. AVIGAN: I just wanted to follow up. One of the points that was made yesterday was the problem of the interim period after signal is detected to get a more precise evaluation, so that you could regulate rationally, and there was some--I wouldn't call it criticism--but there was some concern that this interim period should be looked at strategically to try to limit it, to try to make it as short as possible to get to the answer.

So, part of the question today, it seems to me as I am listening to this, is if you were strategizing, given all the limitations, resource limitations based on study design, implied timelines for, say, an observational cohort study going forward, the time that you would have to wait, how would you think about Step 2 in this

evaluation given that you want to get to the answer in an expeditious way because the public is interested in getting that answer, and the physicians want to move forward. So, I think this is part of the question here.

DR. GROSS: Richard.

DR. PLATT: For me, I am concerned that we are suffering from the problem of looking under the lamp post, that given the information that was presented this morning, most drugs are approved under circumstances that allow for very large safety problems to be present, but unrecognized.

So, I would attach a substantial priority to FDA thinking about how it can most expeditiously exclude important safety problems during the post-approval period. That may be by interpreting the expedited approval rules I sort of floated this morning.

It might be by doing something like providing incentives for manufacturers to do postmarketing studies by insisting that there be clear information available to the prescribing and

consumer community about the upper bound of he limits on serious safety problems, so that it would be possible to know that on the basis of the information available today, we can exclude with reasonable probability the occurrence of serious problems at a rate exceeding 1 in 50, 1 in 100, 1 in 10,000, and that that information be updated as additional postmarketing safety information becomes available.

It seems to me that there is good reason to think that that might have at least as large a beneficial effect on the safety of marketed drugs as the improvements that can be made in following up signals.

DR. TRONTELL: I am intrigued by your suggestion of placing an upper bound on various safety signals, so in a clinical development program, any of perhaps several thousand adverse events are not detected, I am at a little bit of a loss how you would operationalize that.

Would you say in a drug product class where a certain event is known, associated, but not

observed in a clinical trial, you might speak to that? Again, it gets back to what do you convincingly know you don't know.

DR. PLATT: This idea would need some processing, but it seems to me that if the premarketing data says that we observed 100 people for a year, and we saw no serious problems, that the statement you can make is with reasonable certainty we can say the risk of any serious problem is no more than 1 in 40. So, it doesn't have to be class specific.

I think if there is reason to be concerned about specific kinds of problems because of the class in which the drug lives, then, there would be other kinds of statements that you might want to make, but if you start saying we have no reason to be concerned about anything in particular, you can say that having seen nothing in the aggregate, that gives you a certain level of confidence.

Suppose you like that idea and had a standard way of communicating that information and really disseminating it well, you might then have

pretty clear rules about the kind of additional quantitative evidence that you would accept in order to modify that information, what kind of information would you need to be able to say now we say the upper bound is 1 in 1,000, or 1 in 10,000, or 1 in 100,000.

But it might make a difference to prescribers and to consumers to know that among drugs that otherwise appear to be fairly similar in terms of their indications, one can exclude serious reactions at a rate of 1 in 100,000, and the other can exclude serious reactions at the rate of 1 in 100.

That might be useful information to include in the decisionmaking, and it might be a useful incentive to encourage the collection of high quality safety data.

DR. GROSS: Next comment is from Art Levin.

MR. LEVIN: Two things. One is I think there is a distinction between--at least in my mind--between the level of evidence that you might

feel appropriate for regulatory action and what transparency means to some of us, which is we know what you know all through the process.

So, while things may not reach the threshold where you would feel comfortable in taking a regulatory action, why aren't we all sort of privy to what you know at any point in time, and I would think that, at the very least, would say this is completely open and it is some opportunity for prescribers and patients to decide what they want to do with that very preliminary information, so that is one thought.

The second thing is, sort of following up on Richard's suggestion, whether there are circumstances in which again the threshold is not sufficient that you would deny approval, but there are some concerns, and the question is do we need to start thinking about some limited distribution approval, recognizing the tremendous off-label use that takes place.

I mean again with the COXIBs, the fact that these things went from zero to 100 miles an

hour in a huge population of people, not all of whom met the labeled indication, or a lot of them didn't meet that label indication.

The carrot would be that you would get out of jail by doing studies, that you can increase your distribution if you can show that it is safe and efficacious to do so. So, that idea has always intrigued me, that you have a real market incentive to do the work that is needed to be done.

It also begins to recognize the problem that it seems like an uncontrollable, which is the off-label use, but we all know it goes on. So, it is like we sort of hide our head in the sand and say we can't do anything about it, but maybe there is something we can do about it.

DR. GROSS: Curt Furberg.

DR. FURBERG: The question was posed how can we shorten the time from signal until we have the answer, I think that question captures the problem, because it is too crude. It just goes from white to black, and that is a follow-up to what Art said.

I think somehow we need to lower the threshold for action, and when there is a suspicion of a side effect, we need to bring it up and

discuss it, and we had a wonderful example yesterday from that guy who talked about a nurse who had a needlestick and developed liver problem, one case, and proactively, they looked around in Chicago and found another handful of cases.

There was a suspicion of something, that it's not documented that the drug was harmful, but the only way to find out, to find the other handful of cases, is to look for additional cases, go beyond the lamp post and look for it, and get the word out.

The same would apply when the Agency is talking to whatever, Europeans or Canadians, about adverse effects, and there is a signal being discussed in Australia, bring it up in the U.S., because we may have information. We could add information to what they have seen there and either confirm or refute the suspicion.

So, I think there is a pressing need to

lower the threshold for action. We need different levels of suspicion. I mean we have for terror warnings a color code. Why don't you have a color code for adverse effects, and the orange and red suggesting that there is certainty or uncertainty about a problem, and have an open dialogue.

I think that is how we can make more progress, and find the real problems earlier.

DR. MORRIS: There is two issues you brought up I think are very good ones. I like the idea that in terms of transparency, that there be some formalized mechanism made public about how FDA makes decisions about prioritizing signals.

I think that would help a lot because I don't understand it, and having a formal mechanism, maybe a map or something that tells the public what goes into it, but gives you enough flexibility to make scientific judgments on the basis that it might be outside of the box is something you need.

But again making it more public about what FDA sees as priorities, I would suggest that one of the rationales being if the signal is true, what

would be the regulatory action. I mean if true, would this mean removal of the drug from the market, or if true, this would mean some more information on the label, could help prioritize it in the sense of the public reacting to the risk issues.

The second issue that Curt brings up is the disclosure of uncertainty, which is a very, very difficult issue to deal with, and how do you tell the public that there is a confidence interval around what you say. It is very, very difficult.

I know that in certain press releases, FDA does require companies to disclose that the actionability on his drug may be three years away because more study is needed, but finding terms that can explain to the public how credible the information is, I think is going to be vitally important because I think with the new drug list that is coming out, and the idea that these are going to be listed, there needs to be a way of communicating to the public that they can understand what its meaning is, because that is

going to be a very difficult area.

DR. GROSS: I think the most recent discussion is important, but it doesn't address the question, so I am going to keep our nose to the grindstone here, try to get through the questions, and then we can come back to this issue.

With 2(a), I take it there are no additions to what Dr. DalPan said this morning.

For 2(b), criteria to be used to prioritize drug safety signals for quantification in population-based studies.

Does anyone have any comment on how to prioritize drug safety signals? Allen.

DR. MITCHELL: It gets to the issue. I mean I think there was a lot of discussion and clearly, the Agency has given a lot of thought to this, and it is a case-by-case issue without doubt.

But I think that the issue of pursuing safety signals relates again to what Rich said, and I would want to second that very strongly. There is two areas where we get burned as a society. One is where we had reason to predict a safety problem,

but didn't do it, but the other, and, of course, thalidomide is the classic, but there are many other examples, is where there is no reason to predict the safety problem whatsoever.

I think that we would give false assurance to prescribers and patients alike by suggesting that by pursuing the known safety signals, or the likely safety signals, we have assured safety.

DR. GROSS: So, Allen, tell us what you want to prioritize.

DR. MITCHELL: I think a priority really needs to be given to a systematic approach, as Richard said, so I won't belabor that, but I also think that one of the issues in setting priorities that the Agency struggles with is how do you get the data from the time a signal does emerge.

I think there the FDA would do very well to expand its palette, if you will, of contacts and/or contracts, so that when a safety signal comes up, you could even, in theory, send out an e-mail blitz to 20 or 80 or 100 organizations that you know are available to pursue those signals in

existing data or future data.

DR. GROSS: Allen, let's stay on the mark here, prioritize, what criteria for priority?

DR. MITCHELL: I thought that that was responsive to the question, you know, on the one hand, the criteria are going to be incident-specific, if you will, but in pursuing the priorities, you really need to have the resources to hand, and I will leave it there.

DR. GROSS: Sean.

DR. HENNESSY: A couple of things I jotted down for criteria that you might want to consider would be the severity of the event, the safety of the alternatives to the drug including no treatment, the number needed to harm, the number of users of the drug, the strength of the evidence constituting a signal, and the feasibility of following up the signal.

DR. GROSS: Very good. Elizabeth.

DR. ANDREWS: I guess a quicker way of saying some of the criteria that Sean mentioned would be the population impact. If there is an

impact of the event at a population level, for example, a large number of patients exposed, then, that would take a higher priority than a lower exposure level.

The other criterion I would use is that knowledge that the risk-benefit balance would be tipped with the additional information or that there would be some action taken based on additional information. I think that is critically important.

DR. GROSS: Good. Any other additions? Richard.

DR. PLATT: Could I just amplify what I think you included, but I just want to make sure I heard it properly.

When you say "population impact," that is some combination of the number of people affected and the severity of the potential injury. I am not sure I would give much weight to Sean's criterion about how easy or hard it is to address, because I would hate for us to say this could have a huge impact on the public's health, but it is hard to

address, so we will assign it lower priority.

I take your point that some things are easier than others, but I would hate to see us just go for the low hanging fruit sort of methodologically.

DR. HENNESSY: A point well taken, it shouldn't be driven by that, but it's a consideration.

DR. GROSS: Lou Morris.

DR. MORRIS: I would also add to that the likelihood that the hypothesis is true. If it is really far fetched, I would put it lower down than if there is a possibility that it is true.

DR. PLATT: Is it also fair to say this prioritization, that the absence of evidence also counts on the priority score? That is, in the absence of a signal, if the fact that there is very little data--

DR. MORRIS: I was thinking more of the biological plausibility of it.

DR. PLATT: Fair enough, but the fact that some drugs that may, in fact, be causing

substantial harm for which we have no data in some ways should take some priority it seems to me. I think the Agency ought to have an obligation to ensure that, one way or another, enough data is acquired, so that you can be reasonably confident that there isn't a big population impact problem that just hasn't been manifest yet as a signal, because I think that the signal generating capabilities at present are not sufficient to assure you that if there is a big problem, you would know about it.

DR. TRONTELL: Can I ask you to clarify? You are talking then about large population exposure, you were talking about where there was evidence of harm, and I wasn't sure if we weren't sure if there was harm. Could you just say what you just said again?

DR. PLATT: I am saying that a corollary to Elizabeth's principle is that we are often in the situation especially for newly approved drugs that there may be a very big population impact adverse risk that we are just unaware of, so when

you say how do we prioritize signals, I would say that is too narrow a construct, that you would also want to prioritize the absence of information that lets you exclude a serious population level problem.

DR. ANDREWS: Can I take that a step further? So, you are talking about signal, in a way, going back to signal detection, and are you suggesting that there is a threshold of utilization above which there should be some systematic monitoring for systematic signal identification?

DR. PLATT: Fair enough. One way you could tie this together maybe would be to say given all the evidence we have, which includes signals and just limited data, we can establish confidence limits on how safe the drug is, and I think that your prioritization ought to be aimed at establishing acceptable safety levels for drugs that could have a very large population impact.

DR. GROSS: Why don't we elaborate on Elizabeth's point, on signal detection, and make our own question? What would be criteria for

signal detection?

DR. ANDREWS: I don't think we could come up with it at the moment, but I think it has to do with all the same kinds of characteristics that we look at in evaluating signals, so the number of patients exposed, the severity of the type of outcomes, what one would do if substantial risk at a certain level were identified.

But I think it is a useful idea to think about those criteria and suggest that for some exposures in some populations, that there be more systematic quantification of the safety margins, and taking that a bit further, you could look at special populations, such as drugs used frequently in pregnancy, and I think the FDA is already doing that to some extent by suggesting pregnancy registries for certain drugs where there is substantial justification.

DR. PLATT: Peter, if you wanted to maybe assign a work group to take this off line, some of us might be willing to try to think of a coherent answer to your question.

MS. JAIN: I am sorry, Richard, as much as that would be a good idea, legally, we cannot. That is considered a closed meeting, and unless

otherwise fulfilling the FDA criteria, that is not allowed.

DR. GROSS: What kinds of things would you have wanted to consider, Richard, and maybe we need another meeting?

DR. PLATT: I think we are onto something useful here about giving the Agency advice about how it might deploy its own resources and encourage the private sector to rapidly acquire the most important safety information.

DR. GROSS: I think what happens at these kinds of meetings, we get a big, thick book of things to read and then we hear various presentations, we think about it for a day or two, but as you are saying, Richard, maybe it takes more time to think it through, and certainly the interactions that we have in the Advisory Committee give us even more ideas, and maybe we will need to continue to look at this in some manner that is

consistent with the rules.

Does anybody have any other comments? Curt.

DR. FURBERG: Just to follow up, I agree with Rich. I think we need to look at mismatches, as I said before, where the populations studied in the trials that led to approval, if they are very different from the population actually getting the drug, that is, they would flag gaps in our knowledge particularly since we know that the patients in the approval studies are typically younger, lower risk, few exclusion criteria, few concomitant conditions, use of fewer drugs, et cetera.

So, we need to be aware of that and maybe we should also look at the off-label use. That is another group where we have no information available, and we should take that into account when we look for signals.

DR. GROSS: Any other comments? Jackie.

DR. GARDNER: I wanted to ask Curt, I want to be clear, do you mean that you would increase

the priority for the Agency, and postmarketing identification of populations that hadn't been studied, and off-label use, move that up in active looking, that is what I thought I heard you say. Is that right?

DR. FURBERG: Yes, I think some of what I said could be done before approval by reviewing protocol, being sure that the right populations are studied, the ones that are really using the drug or will be using the drug, then postmarketing.

Yes, get into other groups and our frequent users off-label groups with other conditions that have not been studied. There also are gaps and the fact that drugs can be used off label, I am not objecting to that, but we need information on those groups.

DR. GROSS: Robyn.

MS. SHAPIRO: First, I want to agree with the notion that we should think about spending more time on some of these questions because I think that if we shared ideas with more time we would come up with better answers.

Second, while I think the criteria for the prioritization question were good, it is the interaction among the criteria I think that also is

important, so if I go back to ethics for a minute.

We talk about when there is an obligation to intervene so as to prevent harm, ethically speaking, and the severity of the possible harm and the prevalence of the possible harm are criteria that are inversely related and both have to be talked about and thought about in order to come up with the notion about whether you are or are not ethically obligated.

So, it is the interrelationship between the criterion that we haven't begun to talk about, and going back to my first comment, these are just bigger conversations than we have time for right now, I think.

DR. GROSS: Annette.

DR. STEMHAGEN: I agree with all the discussion in terms of the criteria, but in looking at this question again, part of it is saying we have signals based it could be from data mining

where we don't really have a lot of the severity, and so on.

The criteria that we are going to get for severity and impact and populations is going to come from those quantification and population-based studies. I just hear a lot of what we are discussing it seems to me to be much more stimulated case finding. Even in the color coding, all kinds of things, all we are doing is getting a lot more spontaneous reports, we are back in the data mining thing.

So, I think we have to think about the criteria in relation to what the question is saying is we are going to have some signals, when do we go to the next level of study, and it may be that next level of study that is going to give us the things like the severity.

So, I am getting a little confused about the approaches, which seem to me to be what do we do with the data from our population-based studies as much as it is what do we do with the data from the signals. Maybe I am just confused.

DR. GROSS: Why don't we move on to No. 3.

What are the best avenues for FDA to strategically expand its access to data needed to

conduct population-based studies to evaluate the safety of marketed drugs? The examples include Federal agencies, health care benefit programs, and foreign sources.

Much of this was again discussed earlier today and yesterday. Anyone want to add anything? Sean.

DR. HENNESSY: We heard from Dr. Graham earlier today that the cooperative agreements have been tremendously successful and that they have difficulty with resources using databases in house.

The question seems to imply what other databases should be brought in-house. To me, I am not sure that the Agency would be well served by that approach, but maybe by expanding partnerships with outside organizations.

So, I would answer that for both No. 3 and for No. 4. Expand the partnerships with outside organizations like the Cooperative Agreement

Program that had been discussed.

DR. GROSS: Annette.

DR. STEMHAGEN: I know politically, there are all kinds of restrictions in terms of industry, but I would like to sort of bring up to this point in seconding what Sean is talking about, is there is also a lot of expertise within companies who work with these kinds of data all the time, who could probably share some.

I know there were discussions a while ago, and I don't know that anything happened, for instance, of both the industry and FDA working together on good guidelines for database practices, and how do you work with databases, so some kinds of things were even collaboratively with academia, with industry, with FDA, trying to set up some guidelines for how to do this, because I am concerned about the amount of resources within the FDA.

A lot of these data resources, if you don't work with them every day, and really understand the nuances, you can go very wrong in

your answer. So, you really need to be developing expertise for that, and there is a lot of expertise around that we probably are not tapping into that we could tap into on a collaboration.

DR. GROSS: David Graham outlined the resources available this morning. Maybe the people who fund the Agency do get funded on the Department of Agriculture budget or whoever it comes through. Maybe they should be made more aware of just how limited your resources are versus what they would like you to do.

Any other comments on access to data? Jackie.

DR. GARDNER: Following up your point, I think probably the staff worked very hard at making them aware of the limitations. I guess the question would be is there anything that, if coming as a recommendation out of this committee for resources or these considerations might assist their argument, because I don't think you meant to be in the position of telling Paul and Anne that they ought to be clearer with their bosses about

their resource needs. You didn't mean that, did you?

DR. GROSS: I did.

Elizabeth.

DR. ANDREWS: A couple of comments. I think that as we have heard a number of times, doing large database research requires a multidisciplinary approach and quite a lot of expertise and time to do it right, requiring programming and statistics, epidemiology, clinical judgment, understanding of how medical care is practiced in the setting of the particular database.

There is a tremendous amount of time that goes into just writing a protocol and developing the appropriate code lists for exposures and outcomes. So, it isn't something that can be undertaken lightly, so I would suggest that if the FDA plans to develop that capability, do it appropriately because it's a long-term investment, as well, and it is not something that can easily be done a study here and a study there.

The other comment that I would like to make is something we haven't spent much time talking about. I think it is because we are so

familiar with the fact that there are databases that we can turn to, but it is becoming increasingly possible to do very quick turnaround studies using the technology for patient and physician surveys, to get answers more rapidly.

During that time between signal and confirmation, there probably is a lot more that could be done that was not within our grasp or not affordable even a few years ago, so I would like us to at least consider those methods.

DR. GROSS: Comment from the Chair. The CDER and CBER Advisory Committees tend to focus on a particular drug or biologic and then endorse or don't endorse it, and I don't see why this committee can't endorse an approach that would help Office of Drug Safety do the kind of job they want to get done and why can't it have the same impact rather than having a nice discussion among colleagues and friends that may not go anywhere.

Art.

MR. LEVIN: Just two things, to reiterate some things that were said yesterday. One, revisiting the 2000 or 2001 initiative of then Secretary Thompson to create a platform that would allow FDA, CDC, VA, and I think ARC was the fourth

agency and probably could be expanded to other federal agencies to share data, it just seems to me even though that hasn't progressed very far for the usual suspect reasons perhaps, it is worth revisiting.

The second is to go back to the CMS drum beat, because I think what is exciting about that is that CMS is really a payer. I mean it has some regulatory function, but it is really a purchaser or payer, and it has a business case for making drugs safer, you know, making sure the drugs that Medicare beneficiaries are given are safe and effective, and it's an immediate business case.

It is clearly not in Medicare's interests to pay the medical costs of preventable adverse drug events or reactions, it only will increase the

bill for them. So, it seems to me, and then we have in the pink sheet, a rather enthusiastic endorsement of the benefits of the Medicare drug benefit and postmarketing studies being faster and cheaper, I mean whether that is as doable as it sounds from the comments of the Secretary and the CMS administrator remains to be seen, but the point is they are enthusiastic about it.

This may be a unique opportunity understanding all the difficulties in having an agency which has a purchaser hat on and a business case that it can make for themselves to pay the costs of doing this. It will save them money, you know, it isn't simply a cost.

So, the question is how we can sort of piggyback on that to make sure this happened.

DR. GROSS: Richard.

DR. PLATT: One way to sort of embody that would be to change this question and say what are the best avenues for the Federal Government to strategically expand its access, because although FDA is the lead agency, it is not the only

organization that has an interest in this.

I think part of the strategy ought to be to implement Arthur's point by making this a shared goal across the Federal Government because it is no just HHS, it's the Department of Defense. I mean there are a lot of people how have a big stake in it, and I think one of the things FDA could do would be to frame the issues in a way that make it clear that these are priorities for all those agencies, because a lot of this isn't access to more resources. It's making effective use of information that either exists now or will exist in the very near future.

DR. GROSS: Curt.

DR. FURBERG: Peter, I agree with you. We have had a wonderful discussion about drug safety. We should have had it four years ago when the Committee was established. For the first time now we are really discussing the tools and trying to see which ones are working and how can we can develop new ones.

Somehow I share a little bit of your

frustration that we are giving advice, and I don't want to offend anyone, but the feeling is that our advice will go into black box, and we don't know what is going to happen next.

To pick up on what you said, there should be a mechanism, we should find a mechanism, so we can be involved in the next step, to take all this advice and rank them as suggested or maybe help in updating the next version of the Med Watch Program.

We don't need to have separate committees. We could have working groups with FDA staff involved and maybe individual members tackle specific issues, come back with a product to the committee and vote it up or down as a recommendation from the full group.

So, there must be a step to move forward in a constructive way. Here is our real opportunity to have an impact.

DR. GROSS: Lou.

DR. MORRIS: One of the points that I have been confused about over the past couple of days is the point at which FDA undertakes studies versus

when the affected industry undertakes studies, and it looks like there is some overlap.

Help me to clarify when a company is asked to do a study versus when FDA decides it should do it and on what criteria, just so that would be part of the transparency, but another aspect of that is in terms of funding, is the idea that right now I don't think this office gets any user fee--or do you get user fee funds?

DR. TRONTELL: Under PDUFA 3, some component of user fee funds are directed to the Office of Drug Safety for what are termed "periapproval activities."

DR. MORRIS: What I am thinking of is in the next negotiation, the idea of keeping a drug on the market as opposed to getting it on the market be brought up as a way of getting additional funding under user fees. If studies are needed after approval to keep a drug on the market, if that is a legitimate way of expanding user fees for the purposes of undertaking more research.

There is one other suggestion in terms of

types of databases. A lot of the databases we heard about are databases to look at adverse drug events, and there is only one database that we talked about in terms of medication errors, and that is a big question for me is the extent to which the interaction between how a patient uses a drug and the outcomes of that.

We know so little about that, it seems to me, other than the equivalent of a voluntary reporting system, and that if there is a way of getting a better coding system done, so we really do understand more about what causes adverse events in terms of hospital room, the emergency room visits, or something like that, that would be a database that I would think would be worth expanding to make that whole field more scientific and more rigorous, because I think that is an area that is in desperate need for greater science.

DR. GROSS: Curt.

DR. FURBERG: I can't resist speaking up again when I feel that safety is something that is an FDA responsibility, it's an industry

responsibility, and we are leaving out the third party.

If you look at trust as I alluded to earlier, the public does not trust safety information from the pharmaceutical industry. I think there are some doubts also about the trust in the FDA, at least more recently. So, I think it is essential that we get in a third party into the discussion, the patient, probably represented by the scientific community somehow, like people on this committee who can be independent, and then when you talk about transparency, we haven't seen much, and don't expect much on the part of industry and on the part of FDA, but involving a third party, then, you get more transparency into the system and maybe more balance also in the discussion.

DR. GROSS: Sean.

DR. HENNESSY: I am wondering if it's worthwhile to get into the public record whether or not this advisory committee would endorse the need for FDA to have additional regulatory authority to

require postmarketing studies and to enforce postmarketing commitments that it seems from a couple of the presentations that it lacks.

DR. GROSS: I don't know why not.

DR. STEMHAGEN: Maybe we can ask what authority they do have now first.

DR. GROSS: Anne.

DR. TRONTELL: I want to give Dr. Beitz an opportunity because I think some of her talk actually addressed specifically where FDA's authority to require post-approval studies is strongest in other instances.

DR. BEITZ: I just wanted to remind you that there are three rules that stipulate when postmarketing studies are required, and I went over those three. In all other cases, it's a request that FDA makes for studies, but there is no regulation--

DR. GROSS: In all other instances they what? I didn't hear you.

DR. BEITZ: FDA will request studies, but there is no regulation that backs this up except

for the three rules that I mentioned: the accelerated approval, the animal efficacy, and the Pediatric Research Equity Act. Those are the only rules on the books that require postmarketing studies at this time.

DR. FURBERG: It is fine to require studies, but that is just Step 1. Step 2 is to get them done. Right now there are 1,200 outstanding commitments by industry to conduct postmarketing studies, and the FDA lacks enforcement power. There is no penalty if the companies ignore those studies, and the only way we can make progress is to have consequences if you don't deliver, deliver the study and deliver it on time, and that is where the authority should be.

DR. PLATT: Could I re-ask the question, Dr. Beitz?

DR. GROSS: Stephanie Crawford is next, then Richard.

DR. CRAWFORD: Thank you. I am actually kind of following up on what has just been said from the last couple of speakers. I would like to

go on record strongly in support of recommending to the extent possible that mechanisms be explored whereby the Agency could require postmarketing surveillance studies with established negotiated criteria and timelines for new molecular entities that are priority established, as well as the accelerated--I am not sure of all the terminologies, but if it is truly a new molecular entity, I support it, require that postmarketing surveillance studies be done unless, for whatever reasons, the criteria, the sponsors can show compelling evidence of why it would not be needed.

Now, the thing that I am struggling with, and I think a lot of others, is the timeline, I don't know, because we heard from several speakers--I am looking at Dr. DalPan--about the differences in when the serious adverse effects would manifest themselves because there is obviously a big difference in whether they show themselves shortly after the drug product was introduced, whether or not it takes so much longer term years duration to show, so I am not quite sure

what goes into this, but in light of recent activities where there has been so much pressure to bring the drugs on the market earlier, I think there has to be some give and take where there are more mandated studies that follow these.

DR. GROSS: Richard.

DR. PLATT: I would just like to understand how broadly the Agency can interpret the accelerated approval rule, and specifically, since the requirements for pre-licensure exposure allow for such a large undetected safety problem, whether that phenomenon is sufficient to allow the Agency to use the accelerated approval paradigm in the safety context, saying this is really accelerated approval for safety, and therefore be able to require postmarketing studies.

DR. BEITZ: The rules that I mentioned, for which there are postmarketing study requirements refers to only those drugs that are approved under surrogate endpoints, so we are asking actually for studies to be done to confirm clinical benefit and safety data are collected as

part of it.

It is a very narrow definition, and what you are talking about I think is a much broader and very provocative concept.

DR. PLATT: And is the narrowness actually embodied in the language of the rule, or is that just the standard interpretation?

DR. BEITZ: I quoted directly from the language. I think I would just make one comment, if you are going to go down the path of recommending postmarketing studies, that you also consider perhaps instances where one might want to waive such studies, for example, in orphan drug situations where you have very few patients that you can study.

DR. GROSS: Anne, did you have a comment?

DR. TRONTELL: I was going to just elaborate a little bit on the Subpart H approval, which the scope of that rule is to apply to drugs to treat serious and life-threatening illnesses, where available therapeutic alternatives are in some ways limited or unsatisfactory, i won't trust

my recall of the last language.

In addition to the use of surrogate endpoints, it is also in instances where there may be some requirement to restrict distribution relative to the safe use of the product. But it is basically--just elaborating a little bit on what Dr. Beitz said--which is that the circumstances where FDA can apply that, at least as codified now, are relatively restricted.

DR. BEITZ: I just want to make a comment about the second part of accelerated approval related to the safe use and restricted distribution. That part of that rule does not have a study requirement. Only the surrogate endpoint approval portion conveys the requirement for studies.

DR. GROSS: Lou.

DR. MORRIS: But could it? The question is under Subpart H, there is restricted distribution. Could restricted distribution be interpreted as the requirement of a study? Could that be tied together as a means of postmarketing

surveillance required under Subpart H?

DR. GROSS: We have some trouble hearing you. Can you either get closer or come to one of these microphones?

DR. BEITZ: I guess I would say that for many of the restricted distributions that we are envisioning and putting together, that there are studies that are part of those programs, certainly studies to assess their effectiveness over time. So, I think we are doing it, but without the regulation to tell us, but I think we are doing it, wouldn't you say?

DR. GROSS: We are getting close to a critical time in the meeting here. We have one more question and then I would like to go back to what we have been discussing.

Does anybody have any additional comments they want to make on No. 4 as far as short and long term? Robyn. Let's address 4 and get it out of the way, and then we will go back.

MS. SHAPIRO: I will wait.

DR. GROSS: Who wants to address 4? Sean.

DR. HENNESSY: I would say issue RFPs for collaborative relationships both in the short term and the long term.

DR. GROSS: Any other comments?

DR. MITCHELL: Are we on 3 or 4 now?

DR. GROSS: Four.

DR. MITCHELL: I just wanted to make the distinction between the principle that a number of people at the table are speaking to, and making it work, which is where the discussion about Subpart H has gone, and I wonder if, as you have indicated, it may be appropriate for the Committee to take a stand on the principle.

DR. GROSS: Let's do 4 first and then we will do that.

DR. MITCHELL: Okay.

DR. GROSS: Any other comments on 4? Stephanie.

DR. CRAWFORD: Just a quick comment, you will be happy. Short term, to arrange meetings with representatives of the hospital organizations, like we said yesterday, such as JCAHO. I know the

hospitals have a lot of this data, it is just a matter of what incentives would it take for the staff to report it, because I still am a bit uncomfortable at the dearth of inpatient data in the systems.

DR. GROSS: Good. Okay.

Richard.

DR. PLATT: Short term, probably a lot of yield in developing a new and effective communication strategy about the current status of our knowledge about the safety of marketed drugs with a clear statement about what we don't know wrapped up in that, that there is some kind of risk uncertainty built into that.

I think you could do that quickly and it would have a transforming effect on our practice. I will sign onto Arthur's encouragement again to work with sister agencies both to make use of the data that is available and to develop effective plans to use the data that will become available.

Over the long term, I think that there is every reason for the Agency to make much more use

of electronic medical records and to develop automated ways of--automated is the wrong term--to develop much more effective ways to survey selected populations of providers and patients exposed to drugs. There are lots of new technologies that would support that in an efficient way.

DR. GROSS: Any other comments on No. 4? Arthur.

MR. LEVIN: Just what I think is a caution that EMRs are not a silver bullet unless they are designed to be a silver bullet, and we are sort of in this awkward position where there is tremendous activity in electronification of medical records and other things that go on the healthcare system, and if they are not designed from the ground up to do what you want them to do, they don't do it.

So, I would just say there is a sense of urgency here in trying to figure out, if we are going to rely on electronification to make more data more accessible, there had better be some very quick turnaround in figuring out what are the basic elements that need to be there to allow that to

happen, or you will find out that these systems that have been developed won't give you what they could have given you, and it's too late, and the investment has been made, and it will take years to turn it around again.

DR. GROSS: Comment on Question 4? Jackie.

DR. GARDNER: Since we are going on record for things other than what the Agency has handed to us, I would like to suggest that in the short term especially, that the appropriate programming resources be made available to this group, so that they can maximize all these databases that they do have, because if the infrastructure isn't there, then, it doesn't matter what recommendations we make for how they use the data.

So, my recommendation is whatever stops it takes to pull them out.

DR. GROSS: So, we are sort of touching on not only 4, but our general recommendations. So, I think we are done with the questions. Now we have some time to talk about what questions you would

like to ask that haven't been asked, that maybe we can get some answers either now or at our next meeting and what suggestions you would have to improve the impact of the Office of Drug Safety.

Arthur.

MR. LEVIN: I would like to return to something I said yesterday and sort of seconding something that Sydney Wolfe said yesterday. I think there is always a lot to be learned by looking backwards, as well as forwards, and it would be really helpful to take a look back, not just counting, because I don't think it is whether or not there are more withdrawals now than there were before PDUFA, you know, it is really what the risk has been, how many people have been put at risk to me is the metric, not just counting withdrawals pre-91 and post-92.

I just think it would be really helpful to have a transparent look back at where we think things could have been done better. I won't use the word "failure" again, but clearly, things haven't been done as well as they should have been

done, or could have been done, or we would have liked them to be done every time.

It is always good to learn from mistakes. I mean in the errors in quality and safety movement, lessons learned is an important part, and there are columns in medical journals that say what lesson did we learn from this terrible thing we did.

So, you have got to admit you did a terrible thing, but the point is, the positive spin is you are going to learn from that, you are going to make sure it doesn't happen again.

I think we need to do that. I think it would be very informative for me, and I would hope for other people on this committee, to understand what the Agency thinks it could have done better in certain instances, and then how we address that in terms of the recommendations we make on improvements in the future.

DR. GROSS: Arthur, I would echo that. I have actually asked for that for the last several years, and I think it is time that we do this, take

a look at the troglitazone and whatever the other withdrawals or strict risk management programs were imposed, review the circumstance, have it open, look and see what could have been done that might have been more expeditious and more effective if indeed that was possible.

So, I think that would be incredibly instructive. It has not been done to my knowledge, and I think it is very important to do.

Is that a recommendation that most members of the Committee would endorse? Anybody disagree with that? You disagree, Annette?

DR. STEMHAGEN: I would like to qualify it, I think there is probably also good successes where signals were identified, successful interventions were put into place, so let's not just look at the failures, but let's balance it with the successes.

DR. GROSS: Great suggestion.

Could I see a show of hands on that?

[Show of hands.]

DR. GROSS: Okay, with your qualification

included.

Earlier on, a suggestion was made that more enforcement powers should be granted to the FDA to require postmarketing studies as they deem appropriate.

Robyn.

MS. SHAPIRO: Now the lawyer in me is going crazy. We just can't talk about the law or what we think it should be unless we look at it and study it, and see how it has been interpreted, and I think we should do that. I mean there were some suggestions made earlier, yesterday also, about possible changes in the law.

So, I would suggest that we put together a smaller work group to do that kind of work, and maybe, you know, to hold off on making recommendations until we hear the information we are going to get upon Arthur's suggestion and others, but that we put together a work group that before we forward any suggestions about changing the law, we actually read it.

DR. GROSS: That comment is in reference

to?

MS. SHAPIRO: Two things.

DR. GROSS: In improving the enforcement powers?

MS. SHAPIRO: And also the ability to require postmarket studies, perhaps the reporting of adverse events although I realize I was the only one that liked that idea yesterday. But I mean there may be a number of recommendations we would have about the legal powers of the FDA including its enforcement capabilities.

I think that we should do that more deliberatively rather than look idiotic by not having studied this well enough.

DR. GROSS: So, you are suggesting that the FDA present to us a summary of what the law currently says, and then we could go from there?

MS. SHAPIRO: We could, I mean we could get that, too, but yes. I think we need a work group, a smaller group.

DR. GROSS: Well, depending on what Shalini said, I don't know how that could be

constructed.

Anne.

DR. TRONTELL: We really appreciate the opportunity to hear all these different ideas and suggestions on ways to go forward and in no way do I want to try and curtail that.

We have wandered quite a bit from our discussion of data systems and data resources, I understand, in fact, you are endorsing some of what we have already been doing, but I think it is also important to bear in mind that the Agency is undertaking a study with the Institute of Medicine to address some of these safety issues, the larger framework in which the FDA operates in the healthcare system, and I might perhaps invite this committee to consider ways that its efforts, either individually or collectively, might synergize with that activity as opposed to--you have set forth an ambitious agenda of additional studies and activities for the Agency to do--I wonder if you might consider even other mechanisms that some of these thoughts might be put forward.

DR. GROSS: So, how could we liaison with that group?

DR. TRONTELL: I think certainly as that

group moves forward, we could certainly put this committee's expertise in front of that group for possible consultation. Generally, their process involves a series of public meetings, other investigations, and I think that is certainly something that we would be happy to hear if you were so interested.

DR. GROSS: Curt.

DR. FURBERG: I would like to refer you to the bill introduced in the Senate, the Grassley-Dodd bill. That bill has already addressed some of the issue that Robyn raised. They look at the existing laws and came up with specific recommendations for consequences or for these postmarketing studies, this one requirement, there is a deadline for every commitment, which is new. There is no deadline right now. Everything is open ended. That is why we have 1,200 pending.

The other one is financial consequences,

fines if the deadline is missed, and for every month after the deadline, there is an additional fine. I would like to hear someone from Congress, maybe we can get from the Senate, maybe a staffer coming here and discuss that with us.

DR. DAY: I would like to address the problem of appropriate communication of the quality of risk evidence currently available on any and/or all drugs. Earlier, Richard spoke to this and was proposing a way to communicate this, a 1 in 40 or whatever.

First of all, i would like to speak to the need for this kind of communication to be available and promoted to both physicians and patients, and everyone in between, with pharmacists, and so on, but I think that another quantitative measure would be counterproductive.

People already have enough trouble understanding the likelihood of adverse events when numbers are given 1 out of so many, and so forth. So, I think that there are some ways to do this easily enough. There could be a statement either

in the labeling or something about the context in which safety studies or risk evaluations have been conducted, what they are, what sorts of things, and perhaps some kind of scale or linguistic categorization of the quality of the evidence.

I think it is important for physicians, as well as patients. If you have ever been prescribed something in a physician's office, and you ask, gee, what are the possible adverse events, they will often say I haven't heard of any, and sometimes it is taken--or they are just mild, there is no big deal here--there is often mistaking for lack of knowledge of evidence about any AEs and having that be interpreted as there are none to worry about.

So, I think communication about the amount and quality of evidence about potential risks for individual drugs is very important and needs to be addressed and communicated.

DR. GROSS: Jonca, did you want to say something?

DR. BULL: First of all, as you all know,

this is my first meeting as a member of the team in OPaSS, and I just want to say just how rich a discussion this has been. It looks as if you all are done with our questions and that we are pretty much at a point where it looks like we are going to be ending early for today.

A number of the concerns that have been expressed around the table are certainly issues that are critical ones to the Agency. I think there are some concerns to whether or not, within the framework of the Federal Advisory Committee Act, whether or not it is appropriate for this body to discuss, and I am obligated to bring that to your attention, but certainly as private citizens, these are issues that you can certainly bring to the attention of the Agency.

DR. GROSS: That's fine. There were two other people who wanted to make a comment.

Stephanie.

DR. CRAWFORD: My final comment for this meeting would be that in order to minimize the problems with risk assessment and risk management

postmarketing, we need to do whatever we can to help identify these issues pre-marketing.

So, to the extent possible, I would just suggest that the Agency consider identifying people who have a track record and known expertise in drug safety issues to place on each of the current advisory committees, not just within ours, so that at least some of those issues are always brought up as the drugs are being considered pre-marketing as well.

DR. GROSS: The last comment from Sean.

DR. HENNESSY: Actually, I was just told that the comment I was going to make would be out of order, so I won't make it.

DR. GROSS: Okay, not the last comment.

Annette.

DR. STEMHAGEN: I had a follow-up really to Stephanie's comment, which was a question in terms of the amount of interplay between the postmarketing's divisions and the premarketing divisions, because I think we have talked a lot about the importance of starting risk assessment,

risk management thought early on, before the drug gets on the market, and I am wondering about with new changes in organization at the FDA, what the impact of that is, is it going to be stronger, is there an area where it should be stronger?

DR. AVIGAN: Let me just address that from the point of view of my experience as a medical officer who has been at the FDA for approximately five years on both sides of this. I think it is clear that the risk assessment process is a continuum which starts from the time that the molecule is first synthesized to the point where it is marketed and expanded to very large use, so that every step of the way there has to be consideration of risk assessment, evaluation, and what further needs to be done.

So, the short answer is yes, there has always been discussion, but that this discussion, given the high profile of safety issues, needs to be expanded and that there needs to be an operationalized discussion at every stage of the life span of the drug.

One of the issues that comes up with the uncertainty of risk at the time peri-approval, where there is still unfinished business and there

is an imperative to get a report card, let's say, at the first year milestone of the drug around the safety question.

The devil is in the detail as to what specific methodologies can be applied and resources can be applied, in order to get to that point where a report card can be issue in a timely way, and there are different things to consider.

There is methodologic purity on one hand, on the other hand, there is the issue of resources and costs. We heard some of that today. The user friendliness of the databases, the need to accumulate experience of exposure over time, and these need to be weighed with taking into account what the level of concern is.

So, again, one of the things I would like again to have heard from this committee is how they would go about ranking various kinds of methods with regards to this timeline and this need to get

more clarity around risk.

DR. GROSS: Before we adjourn, Shalini has a few comments.

MS. JAIN: I just wanted to say thank you, just like Jonca and the Division have, for participating. We had a very good discussion today. I know that some of you may still have some ideas that you wanted to vent or provide to the Division, so you can e-mail them to me and I will forward them on to the Division as the committee liaison, and I will also provide the name of the people that they will be forwarded to.

Secondly, I sent out a pink sheet on each of your desks, which describes what you need to do or not do with your backgrounders. If you want to have us discard it, you can just put it on your chair. If you would like us to mail it back to you, if you could just leave it with your name, that would be greatly appreciated, so you don't have to pack it on your way home.

Thirdly, the taxis have been arranged. I realize that we are ending early, so I will work

with my team to see if we can get you home earlier.

Thanks again.

DR. GROSS: As Chair, I would like to thank all of you for your input. The FDA asked us here for these two days to make recommendations to them as to how various of their activities could be strengthened, and I hope they take our last few comments for the past hour or so in that light.

It is all to help strengthen excellent activities that you perform.

DR. TRONTELL: Thank you, Peter. Let me extend, not only my thanks, but also for Dr. Seligman, who was unable to be here this afternoon.

I want to thank and acknowledge the hard work of our many presenters, both those from within FDA and those externally, and also to thank the Committee for their very thoughtful and considered comments.

We have put a number of discussion areas in front of you. You have not in any way been shy in giving us your ideas of ways that our data systems and other related systems might be

improved. We will be considering them and you can certainly expect in future discussions of this committee to hear back from us.

So, thanks you, everyone.

[Whereupon, at 2:40 p.m., the proceedings were concluded.]