IMPLEMENTATION OF RISK MINIMIZATION ACTION PLANS TO SUPPORT QUALITY USE OF PHARMACEUTICALS; OPPORTUNITIES AND CHALLENGES: A PUBLIC WORKSHOP

June 25, 2007

Gaithersburg, Maryland

8:30 a.m.

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P R O C E E D I N G S

(8:32 a.m.)

MS. SLUTSKY: Good morning. I understand that most everyone is in the building and making their way through Security. You might ask why such a small agency in such a far away land called Gaithersburg would need security, but we do. So thank you for your indulgence and thank you for taking the time to get here early so we can start on time.

I'm Jean Slutsky. I direct the Center for Outcomes and Evidence at the Agency for Healthcare Research and Quality, which we call AHRQ. And I'm very pleased along with my colleagues from FDA to welcome you to AHRQ for this meeting on RiskMAPs.

AHRQ is a small agency, and some of you may not be as familiar with it as FDA, mainly because our impact is a little bit different. We're a health services

research agency with a very, very broad mission to improve the quality, safety, efficiency and effectiveness of healthcare for all Americans. And within this broad mission, we like FDA are very concerned about the safe and effective use of pharmaceuticals, along with other therapeutics, diagnostic and preventive services.

But really why we're here today is because it's all about the patient. No matter whether you're a scientise, a regulator, a policymaker, or someone else within the healthcare system, what we're all trying to do is make sure that the therapeutics that are provided to patients are safe and effective, and they're administered in a way that makes it easy to provide good healthcare.

I'm just going to spend a few minutes talking about some AHRQ programs and networks. You'll hear more about it later as my colleagues from the agency will participate in different panels. But some of the programs that have a direct impact on RiskMAPS and how they're integrated into the healthcare systems are outcomes and

effectiveness programs, our patient safety programs, and our health information technology. We have networks that are supported throughout the agency that will include abilities to evaluate how well RiskMAPs work.

The CERTS, which are the Centers for Education and Research in Therapeutics, is a long-standing program of which many of the principle investigators and other colleagues who work in the CERTS are here. You'll be hearing from some of them later. Our practice-based research networks, which are primary care-based research networks covering most of the United States, our action network which provides research opportunities within organized systems of care and are our network, which provides patient level research and works with our comparative effectiveness program.

In 2008, this very busy slide gives you an idea of what types of priorities AHRQ has. And you can see that many of these priorities have a direct relationship

to the effective and safe use of medications. And I'll be happy to make these slides available to you if you want.

I do want to emphasize that AHRQ receives a great deal of -- has a great deal of interesting patient safety and health IT. In our fiscal year 2008 budget our request includes 93 million for patient safety and health IT over our fiscal year request. So this slide just shows you that our investment in these two areas for our agency is relatively high.

I also want to highlight a potential home for any innovative RiskMAP activities, which is the Healthcare Innovations Exchange, which will soon go live in June. This is a repository for healthcare innovations at the system level that I hope soon will become something that you all will be interested in using over the coming years.

So in just a moment we'll be talking with each other and discussion because over the next two days, there's probably going to be a lot of different types of

discussions with a lot of different perspectives. So I want to make sure that what we do over the next few days is make sure we listen to each other and understand what we're trying to say. And if you don't, ask questions. And if nothing else, keeping in mind transparency and transformation is an important way to achieve this goal.

So I am going to now move into the very, very important task of laying down some very important ground rules, the first of which is this meeting is being transcribed. And we want you to speak into the mike and identify yourself, or I've been told by the transcriber you'll be identified as voice in the transcription.

Because we're in the highly volatile area of Gaithersburg, you must wear your name tag and security pass cards at all times. And you must return the pass cards to the Security desk at the end of each day. So you'll go through this process again in the morning. What fun. If you need to go to another part of the building

above the first floor, you have to be accompanied by an AHRQ staff member. So please don't try to get into the elevators or the stairway again because this is a highly secured building.

And most important of all, the restrooms are right across the hall there. The women's on the right, the men's on the left. And we do have telephones in the conference lobby. Dial 9 to get an outside line. And this is perhaps the most important message of all. Please silence your cell phones, pagers and other noise-making electronic devices while in the conference center with respect to the speakers and people who are trying to hear and ask questions.

Again, it's my great pleasure to welcome you here to AHRQ. I think this is going to be a really exciting meeting, and again, thank you.

DR. SELIGMAN: Good morning. I am the voice of Paul Seligman, the associate director for Safety, Policy and Communication at the Center for Drug Evaluation and

Research at the FDA. On behalf of the FDA, it is a pleasure to welcome all of you to this important meeting and to thank AHRQ for serving as our host for this workshop.

How to ensure that medical products are used appropriately in ways that they achieve the greatest benefit while minimizing their inherent risks or harms, or harms introduced by the way the product is used, underpin the quality use of all medical products, and particularly pharmaceuticals.

As more medicines have become available, with individuals living longer and taking medicines chronically, taking multiple medicines to treat a variety of conditions for years and even decades, how to effectively manage risks so that they are minimized has become an increasing challenge for practitioners, patients and the systems that support them.

Until recent times, FDA's role has been somewhat circumscribed. Review data submitted from clinical trials

and if safety and efficacy standards are met, authorize the medicine to be marketed, making sure that the professional information or the label is accurate and complete, inspecting manufacturers to ensure that the qualities of our pharmaceutical products are of the highest degree, and then when its marketed, collecting and analyzing adverse event reports and information from other studies.

In May of 1999, with the publication of a monograph entitled, "Managing the Risks from Medical Product Use," FDA formally recognized that as a public health institution, it needed to do more. In that report, and I quote, it stated, "FDA should engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all participants of the risk management system-FDA, industry, healthcare provider organizations, healthcare

practitioners, patients and the public. Only by examining the roles of these various participants can gaps and misallocation of efforts be identified and improvements made."

In October, 2002, with the re-negotiation and re-authorization of PDUFA III, the Prescription Drug Users Fee Act, an agreement was contained in the goals letter that called for the FDA to develop a series of guidance documents for industry including one on good risk management practices.

Subsequent concept papers, public meetings, a draft guidance, a CERTS think-tank, and subsequent CERTs publication detailing the important research issues on managing risk, all contributed to the March, 2005 publication of the Guidance for Industry - Developing and Use of Risk Minimization Action Plans.

A number of basic principles in choosing tools to minimize risk are outlined in that March guidance document that are worth repeating here as this workshop

begins. These include: first of all, maintaining the widest possible access to a product with the least burden to the healthcare system compatible with adequate risk minimization. Second, identifying and defining the roles of those who have the capacity to minimize a product's risks, including physicians, pharmacies, pharmacists, nurses, patients and third-party payers. Thirdly, seeking input from the key stakeholders mentioned above regarding the acceptability and feasibility of implementing such a plan. And finally, acknowledging the importance of using tools with the least burdensome effect on key relationships between healthcare practitioner, patient and the pharmacist and the patient. All these principles reinforce the approach of managing risk as a healthcare system challenge.

The recent Institute of Medicine report in September of 2006 on the future of drug safety recommended that the Center for Drug Evaluation and Research assure that the performance -- assure the performance of a timely

and scientifically-valid evaluations either done internally or by industry sponsors of risk minimization action plans. And in doing so to consider both the burdens and consequences as well as the design and effectiveness of these plans.

FDA recognizes that once a product has been approved that is in general use, that the prescriber is the most important manager of risk. And that good risk minimization not only requires appropriate selection and monitoring of a medicine, but also good communication with a patient who plays a key role as well. And we recognize that all engaged in delivering health care have a role to play in managing these risks. So we look forward over these next two days to constructive discussion. In any involving endeavor there are just numerous learning opportunities.

Taking stock of what we have learned from the application of different levels and types of risk management tools and processes is essential to further

progress in this domain. Our agenda recognizes that good therapeutics requires an approach that involves those who develop, market, prescribe, dispense, pay for and ultimately use a drug product, as well as those who regulate and research these products.

We hope that by the end of this meeting, we will have achieved some of the following objectives. First of all, that we have promoted interactions amongst key stakeholders and increased their awareness of the needs and benefits of working together in this area. That we will have promoted information sharing and collaboration in support of optimal medication use. That in the course of this meeting we will have enlisted additional partners in influencing appropriate use of medications, such as health plans, professional organizations and practicing physicians. And that we will have improved the understanding of the many health care system processes that touch upon drug use so that the interventions can be designed and applied in ways that are both effective as

well as minimally intrusive.

And finally, that we can develop steps that are actionable both for individual stakeholders, FDA, and AHRQ research programs that might initiate further support and refinement of these risk management approaches.

I want to thank all of the FDA and AHRQ staff who have labored to develop this important and timely workshop and to ensure that indeed all parts of the private and public sector who manage aspects of the risks associated with medicines are here with us to share their experience and knowledge.

With that introduction, I would like to introduce our two plenary speakers for this morning. Our first speaker is Dr. Mary Willy. Mary is the team leader epidemiologist and senior risk management analyst in the Office of Epidemiology and Surveillance in the Center for Drugs at the FDA. She joined the FDA in 1998, and prior to that worked for 11 years at NIH as an infectious disease epidemiologist. She has been very active at the

FDA in the development of risk management initiatives and has participated in the evaluation of certain risk management efforts.

Following Mary will be Dr. Brian Strom. Brian is familiar to many of us as the principle investigator of the University of Pennsylvania's Center for Education and Research in Therapeutics Research program. That is not, as many of you know, the only hat that he wears at Penn where he serves as chair of the Department of Bio-Statistics and Epidemiology, the Director of the Center for Clinical Epi and Bio-Statistics and the Associate Vice Dean of the School of Medicine.

So with that introduction, again I look forward to a productive, engaging two days, and I would like to welcome Dr. Willy to the podium. Mary.

DR. WILLY: Well, good morning. I want to welcome you all to the workshop. And I'm going to provide a brief overview of risk minimization action plans. They're going to be the focus of the discussion for the

next two days.

I plan to provide in my talk a brief background about the risk management activities at the FDA, some of which you've heard a little bit about already, a description of some of the important components of RiskMAPs, a summary of the FDA experience with RiskMAPs, and then a general overview of some of the important evaluation considerations, some of which will be discussed tomorrow in one of our sessions.

So let me first provide a short background of the FDA's risk management activities. The FDA has been involved in risk management of drug's risks for many years. Earlier its risk management programs preceded the recent efforts and included clozapine, no-blood, no-drug program. This was implemented in 1990 and was implemented to prevent agranulocytosis. There's a second program, the thalidomide S.T.E.P.S. program, which stands for the System for Thalidomide Education and Prescribing Safety. This program was implemented in 1998 to prevent fetal

exposure.

In the late 1990's, the FDA leadership convened a task force that was asked to examine the current system for managing medical product risk. This group was asked to look at the FDA's role in the system. And as you heard, the task force made a number of recommendations to further improve the agency's risk management activities. And these were summarized and published in May of 1999.

The risk management efforts continued, and in June, 2002, Congress re-authorized the Prescription Drug User Fee Act which included a goal to have the agency develop guidances for industry on risk management activities for medical products. These guidances went through a long process but were finalized in March of 2005.

So there were three guidances that were published. And they include a pre-marketing risk assessment guidance that provides information for industry and how to do good risk assessment practices in the

development of a prescription medical product. The results were pharmacovigilance guidance that was providing guidance in how to do safety signal identification, pharmacoepidemiologic assessment and safety signal interpretation.

And then finally there was a guidance on risk minimization action plans that provided guidance on how to initiate and design a plan, how to select and develop tools that might be used to minimize risk, and then how to evaluate these plans.

So let me first talk about certain aspects of the risk minimization action plan that's described in that guidance. I'll provide you with a couple of definitions, the first one being risk management. And as I said I'm going to refer to how it's defined in the guidance. And risk management is defined there as iterative process that involves first assessing a product's benefit risk balance, and then developing and implementing a plan to minimize the risks that are associated with that product. This is

followed by evaluating the effectiveness of the plan and then making the necessary adjustments. And this process is mostly an ongoing process.

So then we have a second definition, and that is for risk minimization action plan, or sometimes referred to as RiskMAP. In the guidance, a RiskMAP is defined as a strategic safety program that's designed to meet specific goals and objectives in minimizing a product risk while preserving the benefits. A RiskMAP uses one or more tools and will target one or more goals. And it's a program that involves more than just the FDA approved labeling.

As I mentioned, a RiskMAP will include goals and objectives. So what is a goal? It's defined as a targeted specific health outcome that's related to a known safety risk. It's supposed to be stated in absolute terms. And an example might be fetal exposure to drug X should not occur. An objective is an intermediate step to achieving a goal, and it should also be measurable. For example, all females of child-bearing potential will have

a pregnancy test before taking drug X.

A risk minimization tool is defined in the guidance as a cross-sister system that's intended to minimize the known risk. There are several different types of tools that are described in the guidance, and they include education and outreach, reminder and prompting systems, restricted distribution, or also its called performance linked access programs.

So education and outreach is a very common tool, and it works to communicate specific risks that are our concern. This tool should increase the knowledge of key stakeholders such as healthcare providers or patients who can prevent or minimize the risks for the drug. The education can also provide a description of the RiskMAP, it can encourage participation in planned assessment activities such as surveys, and it can also encourage the reporting of adverse events. These are some examples of some education and outreach tools, and they include medication guides, RiskMAP program guides, videos or DVDs,

Dear Healthcare Provider letters and continuing education units.

A second tool is the reminder prompting system. And these tools provide prompting, reminding or double-checking to assess providers in following the appropriate prescribing and dispensing. And these tools can also help patients and their caregivers in the receipts in the use of the drug and ways to minimize risk. So here's a list of some different kinds of reminder systems. There can be physician-patient agreements that have the patient acknowledging that she or he's aware of the drug risk and what behaviors will minimize those risks. There's attestation or acknowledgement forms where a physician may acknowledge that he or she will obtain the necessary testing prior to prescribing a drug. A pharmacy may also be asked to attest to completing certain procedures before they dispense the drug. There's also pharmacy checking mechanisms, sometimes called sticker programs, a pharmacist will check for the sticker to

verify that mandatory risk minimization procedures have been completed prior to dispensing.

So finally we have the restrictive distribution or performance linked access systems. These might be used to limit drug access to targeted patient populations when the product has unique benefits but also unusual risks. Examples can include mandatory registries or enrollment of patients, prescribers, and pharmacists. There can be mandatory patient monitoring that focuses generally on laboratory monitoring. There can be prescribing, distribution and dispensing restrictions, such as the use of specialty distributors.

So as a sponsor develops a RiskMAP, and he considers which tools to use, the guidance suggests that the following be considered. First, that the plan provides for the widest possible access to a product with the least burden, but that it's compatible with the need to minimize risk. That the tools that are selected are based on the available evidence of the effectiveness, that

important stakeholders are included and are asked for input, and that the current technology options and the settings for use are also considered.

So I'm going to provide now a brief summary of the FDA experience with RiskMAPs. But I want you to keep in mind that the information here is meant to be just a general overview, and is no way a complete summary of our experience.

So as I've mentioned there's been an ongoing risk management effort at the FDA, I'm going to keep this summary to a more recent experience. So the Office of Surveillance and Epidemiology started a risk management program in October of 2002. And the review of our activities since that time until December of 2006 shows that there have been 130 risk management plans submitted for review. Now some of these submissions were considered routine risk management, and they required very limited feedback from our office. But other submissions were much more complex. Comments on many of these plans were sent

to the sponsor for the product, and the RiskMAPs were re-submitted with revisions.

As of February, 2007, there were 30 drugs with some type of a RiskMAP. But most involved just a targeted education or outreach program. There are nine plans that were developed after a drug was on the market, and there are 10 plans that involve a performance linked access system.

So as I mentioned, education tools are common in all RiskMAPs, and they may be the primary tool that's used. So education tools are often targeted to key stakeholders, for example, a medication guide for patients. As you may see from the agenda, the focus for this workshop is going to be on the other tools which are reminder systems and performance linked access systems. So I'll review some of the reminder tools and provide some examples.

One of the common ones is limiting the supply of drug, for example, isotretinoin or Accutane has a limit of

30 day supply for each prescription, and I've listed other drugs here that are other examples. For some drugs, there is a no-refill allowed. For a number of drugs, a patient-physician agreement or informed consent is required before the drug can be prescribed. Physician attestation or acknowledgement forms may be completed in certain situations, and also sometimes a patient acknowledgement. And in one case, alosetron or Lotronex requires a sticker before the patient can receive their prescription.

A number of drugs may require the prescriber to enroll or register in the program in order to be able to prescribe. Patients may also be required to enroll or register. There's also some times the need for the pharmacy to register or the treatment site that's going to be administering the drug to register. And sometimes dispensing by specially distributors or central pharmacies is required.

And finally certain drugs may be required to be administered in special settings. For example, dofetilide

requires in-patient hospitalization for the first three days of the initial therapy.

Sometimes mandatory testing is required of the patients before they can receive their drug. For example, clozapine, to be able to receive clozapine, a patient needs to have a white blood cell count done initially every seven days, and then that changes to every two weeks after a certain period of time, and then to 30 days. For other drugs, pregnancy testing may be required.

So at this point, I'd like to provide an example of one established performance linked access system just to give you a sense of, in case you are not aware of, how complicated some of these programs may be. So I'm going to talk about thalidomide, which is a drug that was approved for the acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum, and recently approved for the treatment of multiple myeloma. The safety issue is (indiscernible). And at the time of approval that the RiskMAP was approved,

as I described, this is a S.T.E.P.S. program that stands for the System for Thalidomide Education and Prescribing Safety, and the goal of this program is to ensure that fetal exposure to thalidomide does not occur.

So before a patient can receive this drug, the following needs to occur. First of all, the prescriber, the patient, and the pharmacist needs to register in the program. Then the patient needs to be counseled about the use of appropriate contraception and any important side effects. And a special pregnancy testing algorithm will be followed for women of child-bearing years. This is a description of the pregnancy testing program.

Then the prescriber completes a telephone survey and provides information to the system. The patient will sign a registration form. If the woman is of child-bearing years, then certain pregnancy testing will be done, then the patient completes a brief telephone survey and then takes the prescription to the pharmacy. The pharmacy will also complete certain procedures. First the

pharmacy will contact the care center and provide the authorization number that's on the patient prescription. If all the requirements are fulfilled, the pharmacy will receive a validation number, and that's going to be recorded on the prescription. And then the pharmacy can dispense up to 28 days supply of drug.

So finally, I want to talk a little bit about RiskMAP evaluations. And we're going to have a session on this particular subject, so I won't go into much detail. The evaluation of a RiskMAP is intended to ensure that the resources expended on risk minimization are achieving the desired goal. If possible, the sponsor shall consider pre-testing certain components of a RiskMAP, such as the educational tools in the Phase III part of drug development. And this submitted RiskMAP proposal and evaluation plan should be included, and it should include a time line. And it's always wise to discuss the components of the evaluation plan with the agency since the process can be very complicated.

When evaluating a RiskMAP, the analysis should include evaluation of the performance of the overall success in achieving the goals and the objectives of the program. Health outcomes or surrogates of health outcomes can be used to evaluate goals. For example, using the numbers or the rates of a health outcome may be done. The calculations of rates may be possible when evaluating a performance linked access program because the patient enrollment is generally mandatory, so you get a good denominator that may be used in the analysis. The evaluation of objectives can focus on compliance with important processes and procedures. It may also include assessment of comprehension, knowledge and desired behaviors.

Different types of data may be used when you're evaluating the programs. Drug use can be used to look at patterns of prescribing and use. Population databases might be used to assess the outcome or to infer certain physician or patient behaviors. And sponsor databases may

be used to monitor outcomes and process measures. Surveys may also be used to assess patient and healthcare provider knowledge and compliance with the RiskMAP procedures.

How will we use this information? It can be used to identify the need for modifications of the current RiskMAPs. But the information may also be used to share with others so that we may have lessons learned. And hopefully in the future there may be some way to communicate that to some kind of website.

Well, what do we know about RiskMAPs, how effective they are? There is some evidence that some programs are effective. The clozapine program will be discussed tomorrow. And there's some evidence that that has been successful and thalidomide as well. But for the most part, the programs have been relatively small, and so it's been difficult to evaluate the effectiveness of these programs.

And there's certainly information that we don't know. How many patients could benefit from a drug that --

to find the access to the drug so challenging that they don't take the drug? How many prescribers decide to use other products with similar indications because those products don't have a RiskMAP? And, how many patients go outside the RiskMAP to a product such as on the web?

So in conclusion, I've described a little bit about the history of the risk management program at the FDA. And as I've described, although the numbers of the plans has increased, their actual number remains relatively small. We see a variety of tools that are being used in these approved plans. And I guess we all appreciate here that the evaluation of on-going RiskMAPs is extremely important if we're going to determine what goals are being met or whether there's a need for some type of modification. Thank you.

DR. STROM: Great. Thank you. What I'm going to be talking about is really context for the issue of RiskMAPs. This is my conflict of interest disclosure firstly. It's also an eye test. It's a -- what I'm going

to be talking about again is improving drug safety systems approach. Brief introduction and a little bit of a description. Everybody here certainly knows the current system. We have limitations in the current system and the proposal for the future in terms of the use of RiskMAPs. My purpose is really to place the newly developing program in RiskMAPs into a context of the health system or broadly as an academic. I'm obviously not personally involved in regulatory decisions.

First, as a matter of introduction as Sir William Mosler said, "a desire to take medications is perhaps the greatest feature which distinguishes man from other animals." On the other hand if you think of the -- if you look at the newspapers nowadays, it might instead remind you of this quote from Oliver Wendell Holmes, "If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes."

Obviously the goal here is that it not be the

case. Yet patient safety and medical errors are an enormous problem. Using data reported in the IOM report, the iatrogenic injuries cause up to 180,000 U.S. deaths per year and disability and prolongation of hospital stay in another 1.3 million. Medical errors caused between 44,000 and 98,000 annual deaths, more than motor vehicle accidents, breast cancer and HIV, and costs between $17 and $29 billion a year. It's an essential part of obviously why AHRQ has a major focus on patient safety as a focus.

These data have been criticized. The point isn't whether it's this big or it's half the size. The point is it's big. But this is a major problem that needs addressing. As part of that, adverse drug events are by far and away the most common iatrogenic causes of patient injury.

Well, what's our current system? Again talking briefly because this -- knows very well we did pre-clinical studies, three phases of pre-marketing clinical

studies, and then post-marketing for Phase IV testing which is not always required. In general, Phases I to III have traditionally included between 500 and 3,000 patients. And I'll come back to the implications of that.

In my sense, working in a number of products and with a number or organizations, is that in the recent couple of years, Phase III testing has been prolonged in many cases adding numbers and adding time associated with that.

What are the data sources for pharmacoepidemiology studies? They're listed here. Spontaneous case reports of adverse reactions, aggregate population based data sources, computerized collections of data from organized medical care programs, data specifically collected for pharmacoepidemiology on an on-going basis, the old Boston College Drug Surveillance program, and the Sloane epidemiology units case controlled surveillance, existing data collected as part of other ad hoc studies. It's where somebody happens to be doing a

study that has the answer to your question in it, and data collected de novo.

I'm just going to very briefly talk about two of these. The first is the spontaneous reporting system. These are obviously the FDA MedwWatch System relied -- this is relied on for hypothesis generation, but it's really a 1950's era system which has been computerized. It clearly is much better than what is in the 1950's, but I think it's very important to keep in mind in errors or varies for vaccines that the plural of anecdote is not data. These remain simply anecdotes. They remain sources of hypotheses, and you need to go to other sources of data to confirm the hypotheses.

The other, just to briefly talk about, is computerized collections of Medicaid billing -- of billing data, Medicaid or otherwise. Here data come from the pharmacy, the pharmacy has to justify in dispensing a drug, has to justify the bill with information about the drug. The physician -- patient goes to a hospital for

medical care, go to a physician for medical care. They have to justify those bills with the diagnosis. Those aggregated data, drug information and diagnosis information ordered in chronologic order represent an enormously useful research tool which has increasingly been used over the last couple of decades by our field of pharmacoepidemiology to test hypotheses.

The key problem of historical pharmacoepidemiology, however, is as shown here. As I alluded to adverse drug events are the most common iatrogenic causes of patient injury. But most are the result of an exaggerated but otherwise usual pharmacologic effect of the drug. Yet historically these have been ignored by pharmacoepidemiology as they don't represent the focus of commercial and regulatory interests. Historically the focus has been on the rare idiosyncratic adverse reaction to a drug rather than how do we rationalize use of drugs and use them more appropriately in a way that is safer for patients. So it's sort of like

this. It's less than one in 10,000; something like 1 in 14,000 gets these side effects. Hardly anybody gets these side effects. They're extremely rare. You should be very proud.

Obviously the people who suffer them are not very proud. Those have been historically the focus of our field, and it's wonderful to see the beginning shift in focus to talk about focusing on how physicians use drugs and how to optimize the patient outcomes through the use of drugs. Have another -- do you remember which symptoms you began with and which are side effects.

Unfortunately this is all too common. Physicians don't always use drugs in an optimal way. I can't tell you the number of patients -- I'm a general internist clinically. If they read a quote from me in the newspaper, I suddenly get a number of patients who come to me or who were referred to me, and they come with a bag of medications saying there's something wrong with me. It may be related to my medications. Doc, can you help me.

And I look at this bag, and the first thing I do is I say let's start by stopping them all. And once I pick the patient up off the floor in shock, if they're willing to do that, what you track back is a patient being put on one medicine and suffering a side effect from it. And instead of it being stopped, they're put on a second medication for the side effect. And then a third medication for the side effect of that. And it is an extraordinarily common sequence. And once you take them off all the medicines, they come back a month later and go, Doc, I haven't felt this well in years.

Physicians don't always know properly how to use their drugs. And it's very important -- it's impossible for physicians to keep abreast of all the available information. And it's very important that we provide information, and sometimes more than information, so that our patients can better benefit from their drugs. So it's of course with any prescription drug, there are side effects. All drugs have side effects. Our goal is we

need to increase the benefit from the drugs and decrease the risk of those side effects.

Well, let me shift gears and give you a little bit of context. I'll talk more tomorrow about a program we have underway in our hospital as an example. So we have a program that we call our Drug Use and Effects program that has three primary goals. One is our adverse drug reaction reporting, second is drug use evaluation, and third is pharmacy cost containment. Obviously our hospital cares most about the third.

But the goal here is to collect adverse reactions and to change the way the physicians in our hospital practice medicine in order to optimize therapeutics within our setting. It was hospital based. We've now extended it as well to outpatient practice. This, along with formularies, is the kind of thing that is present throughout the country now as more and more people try to apply epidemiology to try to rationalize drug use and improve the way drugs are used.

So in our case, you can see we went from almost no adverse reactions a year. There were actually 10 -- in the graph, I've shown more than that because you wouldn't see the bar -- to about 5 or 600 adverse reactions a year when we started systematically collecting them.

We also have increasing use of IT based interventions to try to rationalize the use of drugs. We sent out immediate alerts in our medical records system with withdrawal of a number of drugs that were withdrawn identifying four prescribers, their patients who were on those drugs, so they can contact them and tell them. We've also delivered specific warnings regarding other drugs.

Other IT interventions and evaluations under way. Here's just a few of them, and again I'll -- tomorrow when we talk about evaluation, I'll talk about the last one in more detail. But we've randomized trial underway looking to control the use of long -- restrict the use of long-term metaclopramide, a study of warning

fatigue because as part of this IT system, docs are now getting lots of warnings and blowing right by them therefore. And so the question is how many are too many when people won't pay attention. Warfarin, NSAID interactions, insomnia, and hypnotic use, appropriated insomnia hypnotic use, and the warfarin trimethoprim sulfa study that I'll talk more about tomorrow.

Lots of future interventions. We're now considering ace inhibitors and lipid lowering in diabetics, insufficiently used, anti-coagulation and atrial fibrillation. Not always used, and not always used correctly. Anti-rejection therapy in transplant patients, Beta blockers and aspirin use, post-MI, drug selection in hypertensives, drug use in congestive heart failure, osteoporosis, prophylactics. These are just a few.

My point in showing these is normal medical care now involves lots of interventions and lots of efforts in order to try to rationalize the use of drugs. We've moved as a society beyond the point of saying put a drug out

there and leave it up to the doc. People realize physicians can't properly use many of the drugs that are out there. And the medical community is putting in place already many interventions as part of usual medical care in order to try to control that.

Let me shift gears again. The CERTS have already been mentioned a couple of times. I just want to mention again the CERTS are -- I don't have a pointer, but at the bottom right you see the Centers for Education and Research in Therapeutics. We have the privilege of being one of them. There are others as well. This is an AHRQ program in partnership with FDA.

The goal of the CERT program is really to begin to fill that gap, to really rationalize the use of drugs, changing the way physicians use drugs in order to be more rationale. So, for example, our CERT is targeted with anti-infectives, and so the goal is to try to use -- get physicians throughout the country to use antibiotics and other anti-infective drugs more appropriately, both -- not

using them when you don't need them, but also using them correctly when they are needed correctly.

And so again another national program targeted toward trying to optimize the use of drugs so patients can better benefit. Increasing the probability of benefit, decreasing the probability of harm. That was a slide that didn't transfer from the Mac to the PC. But this shows where the CERT centers are scattered throughout the country.

Well, what are the limitations in the current system? The first are that in pre-market and clinical trials, carefully selected subjects may not reflect real-life subjects in whom the drug will be used. Second, is that the study subjects may receive better care than real-life subjects. Third, is the short duration of treatment apparent in pre-marketing studies. Fourth, is the lack of information on comparative effectiveness. All of these are things that remain to be evaluated after marketing.

In addition, increasing development costs leads

to an increasing need for immediate huge sales and the desire for so-called blockbuster drugs and aggressive marketing practices that go along with that. Yet this is in the context of development programs that traditionally have had on the order of 3,000 patients. The 3,000 patients you reliably know about adverse reactions that occur 1 in 100. You do not reliably know about adverse reactions that occur 1 in 1,000 or less commonly even if they are very serious. So that there is an inherent gap. These are inevitably questions that are left after drugs are marketed.

What are some of the implications? Fifty-one percent of drugs have label changes due to major safety problems discovered after marketing based on the GAO study. Twenty percent of drugs get new black box warnings after marketing. Four percent of drugs are ultimately withdrawn for safety reasons. I call these opportunities, not problems, because to me these are the successes. These are where we discovered them. What I worry even

more about are the ones we don't know about because they haven't been discovered.

Other issues in the current system. There's no incentive for sponsors to complete promised post-marketing safety studies, and that direct consumer ads lead to overuse of the drug by patients for whom the use of the drugs is not yet compelling in order to try to achieve early on blockbuster status for a drug when in fact you don't really know what the drugs uncommon effects are. Then that effect is the public misunderstands safety. It thinks drugs are safe, and that post-marketing discovery of an adverse reaction means somebody messed up, not realizing that's in fact a normal built-in part of the system.

Second is increasing concern about the safety of our drugs and the publicity associated with that. And the net over-reaction is an increase in pre-marketing requirements with delayed access to drugs and drugs being dropped from development.

Well, what's my proposal? The key is the recognition of the balance between risk and benefits. When you make a choice, the menu, so to speak, there's a societal menu that FDA is choosing from. There's a menu of drugs on the market that physicians are choosing from. There's recommendations of their patient -- recommendations of their practitioners, that physicians -- that patients are making. There is a choice between risks and benefits, and you need to keep both in mind. When you look at the context of side effects and safety problems, it has to be viewed in the context of benefits. And the goal is how to better balance the two.

That is the role of risk management. We have -- it's providing -- there's two general -- broad categories of risk management, and this sort of much more briefly summarizes what Mary presented. One is systematic information, sharing or actions undertaking to improve the balance -- I'm sorry, the definition -- to improve the balance of a drug products benefits relative to its risks.

And then two broad categories. One is informational and the other active or administrative programs.

So risk management is sort of like this on the left. There's risk perception as they notice that rock at the top of the hill. In the middle is risk assessment that they argue with each other whether they have to do anything about it, whether there really is a risk. And on the right is risk management, as the rock comes down and they are doing something about it. That's what risk management is about is doing something about risk that are there. They're inherently there. The question is how despite them do we improve patient care.

So the general tools, informational tools, including product labeling, patient information materials, medication guides, patient package inserts, and targeted healthcare provider education, and then active intervention, constraining patient use, constraining healthcare prescribing or dispensing, restrict the manner of product distribution or ultimately withdraw marketing

status, which is a way of risk management. And again Mary talked much more about these.

There are many drugs with risk management plans, and again Mary gave a more definitive and up-to-date review of these. Here's some examples. The goal in these is to increase the benefit end or decrease the risk. Or in some cases, simply limit the use to those most likely to benefit. Sometimes the only way to do this is to introduce a hurdle. Clearly what you prefer to do is to steer the drug toward the patients likely to benefit, or steer the drugs away from the patients likely to be harmed.

If you can identify the patients most likely to benefit, that's great because you can steer the drug accordingly. If you can identify the patients most likely to be harmed, that's great because you can steer the drug accordingly. If not, sometimes all you can do is put up a hurdle to make the drug hard to get so only the people who really need it will access it. Those are all approaches

that are used, the last thing, least desirable, but what sometimes necessary given the available data.

The other goal is to preserve access to drugs that otherwise would be lost because without these programs, the risk benefit for the drug isn't beneficial, and the drug wouldn't be on the market at all. Again a cartoon that didn't convert. This is showing again the benefit risk, that the FDA has to balance it, the provider has to balance it, and the patient has to balance it.

Well, the evolution of -- I'd like to talk just a minute in closing about the evolution of therapeutics. We're really moving as a field and as a society. Historically we've had an empiric choice of therapy. We've talked about on average over a total average patient population, does the drug work, and on average, what are its side effects, and then on average, are the benefits worth the risk of side effects. And we have focused on the process really a turning of the average because different people are different than those averages. Some

people are responders, some people are not. And their traditional approach to making these decisions ignore that. It has to ignore that. And in the process, you end up giving the drug to people who aren't going to benefit, so they suffer the risk of the side effects, yet they don't benefit. And you give the drug to people who are going to suffer harm who might have been possible to steer away from that.

As a move toward addressing -- to solving that problem, we increasingly now use statistical predicted models of patients who are likely to benefit or likely to harm. And there are many examples of that, but the goal is to try to statistically identify -- again it's still on a population basis, but to try to increase the likelihood that a patient is likely to benefit and decrease the likelihood that a patient is likely to harm.

Clearly where we're headed and where we would like to be is personalized medicine where you can tell in any given individual who's likely to benefit and who's

likely to harm by testing them genetically. There's a couple of -- few examples now where that's the case, but as of yet, very, very few. And yet this has been -- this includes the Holy Grail and includes something that we would like to get to.

I think it's important to realize that RiskMAPs are in between -- a step in between there. It's a step better than just statistical modeling because you're now both providing information to the provider about who's likely to benefit and who's likely to harm. And in some cases, enforcing, restricting who's going to get the drugs in order to increase the likelihood of who's likely to benefit and who's likely to harm.

It is an extraordinarily rational step on our way to personalized medicine where ultimately the goal is to know in any individual should they get the drug or shouldn't they get the drug. The better we are at doing RiskMAPs, the closer we will be along that spectrum. And so it is a perfectly logical next step while this Holy

Grail that has been imminently on the horizon for the last decade continues to be developed.

So as a summary, to me RiskMAPs are key potential contributors to the public's health. The goal of RiskMAPs are to improve the risk benefit of balance of drugs, increasing the risk -- increasing the likelihood of benefiting, decreasing the likelihood any given patient is going to be harmed. In the process, it allows drugs to remain on the market that might not otherwise be on the market.

Like any intervention, RiskMAPs need to be evaluated for their safety and effectiveness. We'll have a whole session tomorrow on evaluation, and I'll give you an anecdote from our own experience, a pen that I think makes that very poignant. Interventions are therapy, and like drugs, they require evaluation. We need to know what their benefit is as well as their harm is.

The use of RiskMAPs is consistent with the trends underway in the nation's healthcare system to

improve patient safety. There's lots of such initiatives already underway. RiskMAPs are a natural step. They are also a logical next step toward the eventual goal of personalized medicine. Decisions usually involve risk we're choosing -- when we choose drugs between risk and benefit. And the more we can tailor that therapeutic decision to the individual patient, the better the patients -- the better off patients will be. Thank you.

MR. SELIGMAN: Thank you, Brian and Mary, for excellent presentations. We have time now for any questions that any of the audience would have for either Brian or Mary. Questions, comments? If you do, would you mind finding your way up to one of the microphones just so we can -- the transcriber can hear you? And Brian and Mary, why don't you come on up, and we'll convene an impromptu panel here.

MR. MALABISKY: Yes, hi, good morning. My name is Kevin Malibisky (phonetic) from (indiscernible). Two very nice presentations. Thank you very much. Dr. Strom,

a question for you. I like the idea of being able to try to assess or at least evaluate some aspect for a potential RiskMAP in a late stage development program. But how do you potentially go about addressing any ascertainment bias that may come about through that type of an implementation?

DR. STROM: Can you clarify what you're meaning by ascertainment bias in that?

MR. MALIBISKY: Sure. If you're going to assess, potentially assess the function of a RiskMAP, or certain procedures that you're going to impose at a RiskMAP in a late stage development program, potentially you have a bias that you may be introducing by focusing specifically on those key events that you're going to be looking at, looking to minimize or manage on a post-marketing setting.

So for instance, if you have a drug that may have a certain set of adverse events, and you're looking to manage those adverse events in a post-marketing

setting, but you want to get as much information in the development program on those events, you want to query, or you're going to potentially query patients more for those types of events that characterize those events better, and that may in fact introduce additional ascertainment bias which may in fact bias the results of the program that you're trying to eventually manage.

DR. STROM: Yeah. Let me respond three ways, see if this helps. Firstly, I think it's important that all RiskMAPs be evaluated, and those evaluations be made publicly, ideally in peer review literature as part of that. I think part of where we learn whether the RiskMAPs work is from the prior ones and deciding accordingly.

Secondly, I think certainly a significant risk in trying to evaluate RiskMAPs as part of a Phase III development process is that of generalizability. It's not the real world. And what people will do in the context of the controlled setting that has to be the case in Phase III isn't necessarily what they'll do in the real world,

which is part of why it's important to evaluate RiskMAPs in the real world.

The issues -- but thirdly, I would design -- well, I got four comments. Thirdly, one of the things my fellows get tired of me hearing is the question is what is the question. And I think it's hard to answer questions in generality as opposed to telling it individually. Often it looks like there's a general problem, but in the specific situation, you can find a solution to the situation.

And part of the solution, my fourth comment, may be that you're really talking about a different study during the pre-Phase III stage, development stage, where you would evaluate the intervention and look at what patients' behaviors are in response to that intervention. So you wouldn't do it as -- most likely you wouldn't do it as part of the actual pivotal trials. You would do it as a separate study evaluating the intervention, utilizing any intervention -- RiskMAP is an intervention -- is like

a drug. It'll have risk, it'll have benefit. And like a drug, it should be evaluated. Almost surely that will require a separate study in order to evaluate that as opposed to doing it.

MR. MALIBISKY: Are we looking to do that pre-approval or post-approval, or during the review process?

DR. STROM: Well, again, I'm not a regulator. That's up to you guys, but certainly I would want to have as I mentioned all RiskMAPs done, put in place, evaluated post-approval. Were I a regulator, I would love to see an evaluation done either of a prior example of that, or a pre-marked, pre-approval evaluation done before approving one to know that it worked. And there are all sorts of ways you could evaluate the specific intervention not even in the context of that drug in question in order to differentiate. But clearly were I a regulator, I would be much more comfortable approving a RiskMAP if I knew it was likely to work.

MR. MALIBISKY: Yeah, and likely from an

industry perspective as well, I think that's the direction that at least some of us, most of us, probably are moving to before embarking on some arduous risk management program to at least have some evidence that what we're proposing will actually work and to have evidence from either a Phase III program or an on-going Phase III-B program (indiscernible). Thank you.

DR. STROM: Sure.

DR. SELIGMAN: Yes, sir.

DR. METZ: Craig Metz, GSK. Just to pick up on that last point. You know, unfortunately because as you've said earlier, pre-approval clinical development programs are fairly small. Many of the risks that we may need to develop the RiskMAPs about aren't going to emerge until in the post-marketing surveillance thing. So it's going to be the rare and happy situation where we can do things proactively as you suggested. I think the place where we need to spend more time, however, is on patient and physician education around the core elements of the

prescribing prior to marketing. And I think we need to spend a little more time there.

But one of the questions that I've got for you, Dr. Strom, is around the adverse event situation, how much of that is medication error, the wrong patient getting a drug, the wrong dose being given to a patient, and how much of that -- of those adverse events are really associated with appropriate product use. And what's going on with the CERTS as far as taking care of those process related issues around, you know, inappropriate product use?

DR. STROM: Yeah, couple of responses. Certainly rare adverse events as you alluded to will not be known about after marketing. But rare adverse events are also -- and this relates to your second question. Most adverse events from a public health point of view are not the rare adverse events. Most of the adverse events from a public health point of view are the common adverse events often related to a drug used incorrectly. And so

it's the pharmacologic effect of the drug that causes the most public health problem as opposed to the rare idiosyncratic effects of the drugs.

So the purpose of most RiskMAPs wouldn't be to try to prevent the rare adverse event that in fact you probably don't even know about yet. The purpose of the adverse -- of the RiskMAP would be to try to prevent the pharmacologic adverse events that you do know about as of the time of marketing. Or those medication errors, in many cases by definition they would be medication errors, but that the question still is that happens, and that's done.

And whether or not you want to enforce the drug label, which is sort of implied in what you're saying, I think depends. I think on one level you don't want to restrict physician use that is rational. You do want to restrict physician use that is high risk or may not be rational. And that's the kind of judgment that needs to go into whether or not to build a RiskMAP in any given

situation. In the thalidomide situation, it's easy. If you don't want it to be given at the beginning of pregnancy, you build a RiskMAP around it. Without an effective RiskMAP, that drug's risk benefit is not worth having. In most drug situations, the pharmacologic effects of the drug are not so harmful that it's problematic.

On the other hand, if you look at drugs withdrawn from the market, many of the drugs that were withdrawn from the market ultimately were because physicians weren't using it correctly. And so RiskMAPs really are useful in protecting the drugs as well as protecting the public's health.

MS. HAIRE: Doris Haire, American Foundation for Maternal and Child Health. I have attended many FDA advisory meetings on obstetric drugs that have not had any representation from pediatricians or pediatric neurologists. In light of our problem of autism and other neurological problems among our children, I do hope that

pediatricians and pediatric neurologists will be involved in the RiskMAPs for obstetric related drugs. Will we be assured of this along the way?

DR. WILLY: Well, when we're looking at the development of different products, we have teams from different offices that are usually involved in the review of the products. When it comes to the advisory committee discussions when they're putting together the representation for that committee, they try to bring in everyone that would be relevant. So I can't really speak to specific drugs, so I don't know if anybody else has anything else to say?

DR. STROM: Well --

DR. WILLY: But they do have a pregnancy group office in FDA that's very involved with RiskMAPs.

DR. STROM: But I mean your point is well taken. I mean when we develop RiskMAPs, we want the right people at the table who have the expertise in that clinical area to help us in ensuring that, you know, the practitioners

are represented as well as the patients in helping to design a program to effectively manage risks. And I, you know, probably would be the first to admit that there are probably times when we don't have that right representation, but we certainly strive to achieve that.

MS. HAIRE: Thank you.

DR. SELIGMAN: Yes.

MR. KAHN: Sidney Kahn, Pharmaco-Vigilance and Risk Management, Incorporated. I would like to try to continue the discussion that emerged about managing risks that are known. The Lazaroo (phonetic) Paper in (indiscernible) in '98 presented some -- quite alarming statistics on the number of hospital admissions and even fatalities as a result of essentially knowing the effects of drugs as Professor Strom has mentioned.

I was recently at a presentation given by -- and there were some criticisms of that paper based on the fact that it was old data, and there were some issues with it. However, I was recently at a presentation given by a

Professor Peer Muhammad (phonetic) from the University of Lester where his group studied approximately 40,000 hospital admissions in the Lester teaching hospitals within the last few years. And I was really surprised to find that the rate of hospital admissions for serious adverse drug reactions and fatalities was actually very, very similar to that in the Lazaroo paper. I believe it was something like 6 percent of hospital admissions were due to adverse drug reactions, and about one sixth of those resulted in fatalities.

Now what was striking about those statistics was that all of these were known adverse reactions. These were not the QT prolongations and torsade's. This was not heparin toxicity. This was not agranulocytosis. This was bleeding from warfarin overdose. This was GI bleeding from NSAID use, this was parasitamol overdose.

So the question I would raise from a public health perspective is while not negating the importance of risk minimization programs for particular products like

thalidomide that have a very defined benefit in a particular population, but really is this where we ought to be concentrating our efforts when, you know, the problem is so much larger from what we already know?

DR. STROM: Exactly. I mean thank you for the comments. I certainly agree with you. I think it's important to realize there's no silver bullet here. There's no one solution that is going to solve everything. I think the RiskMAPs are a way of addressing exactly what you're saying for newly marketed drugs where there are adverse reactions that you know about, and you're trying to steer the drug to the people least likely to suffer the adverse reaction and more likely to benefit from the drug.

That doesn't in any way address the warfarin bleed, the heparin bleeds, the acetaminophen from poisoning. Traditionally those have been in our hospital, the number one, two and three adverse reaction. Recently the number one adverse reaction has shifted to hypoglycemia with a change in the new insulin's and the

way people are using it. And so it's a -- clearly that will -- there's a lot of other work needed besides just RiskMAPs. The CERTS are centrally involved in that in trying to rationalize the use of drugs, particularly older drugs as well.

There's an enormous amount of work needed here. The entire patient safety movement that AHRQ has been central in is really focused on exactly that movement. RiskMAPs are only a small part of it, but it is a central and critically important part of it.

MR. TRILLER: Darren Triller from Ipro. I'm a pharmacist. And I just want to wholeheartedly agree with some of the points that I believe the RiskMAPs that target the drugs that were listed only affect a very, very small percentage of the patients. And I think there's multiple papers. And Gerwick's also showed that, you know, two thirds of the most highly preventable serious adverse drug events are the drugs we know, so it's been said. So I guess I would just argue again that the whole system needs

a change in which the variation of a whole system needs to be reduced.

And the idea of putting forth goals, I guess I'd suggest one goal for the health system would be something along the lines of every patient will demonstrate a basic understanding of a drug they're going to take before they take it. And that that understanding would be somehow documented.

In flying down here, you're able to register to get on a flight using touch screens, everything else you can check out of the grocery store. As a pharmacist I think that it is now well within the realm of practice to document at the time of use, either prescribing the doctor's office, discharge from the hospital, at a pharmacy, that a patient understands what a drug is for, what the risks are, what to look out for and what to call for.

And New York State has a mandatory counseling law that every patient must be counseled on these new

drugs. And counseling consists of everything from do you have any questions to a half hour sit-down. The variation is huge, and I just think it's time to address, in addition to RiskMAPs on specific drugs, reducing the variation in overall drug prescribing and documenting when it occurs so that we can actually create a data system that could follow this stuff.

DR. STROM: I just want to pick up on one comment you made and follow up of something that Mary had said too. And it's the only thing I think of Mary's talk that I disagree with, which you both said that the current RiskMAPs affect a small number of people. I'm not so sure. There'd only be a small number of people who were involved, but that may be the success of those RiskMAPs that in fact if it were not for them, there might have been a large number of people exposed to those risks. It's the classic problem of preventive medicine. You never know about the problem that didn't occur. But I wouldn't underestimate the impact. Again a low use of

drugs that are highly toxic is in fact a success. And that doesn't mean that there weren't a lot of people who would have been exposed were it not for that.

DR. SELIGMAN: Yes.

MS. ROBINSON: Good morning. Patricia Robinson from Johnson & Johnson. Thank you for those very nice presentations. Could you please clarify who from the FDA will be involved in the review of a risk management plan beyond the division level?

DR. WILLY: Well, when a RiskMAP comes in, it goes to the division that covers the drug. And then our office, which is the Office of Surveillance and Epidemiology, has a special group that will be participating in that review. And then there may be other groups as well that are asked to participate, depending on what's submitted.

MS. ROBINSON: So are all the other groups just dependent upon the drug or the choice of the division? Are your two groups the division and then Office of

Surveillance and Epi the only two mandatory groups? How about the Office of Policy, for example?

DR. WILLY: I don't know, Claudia, if you know where the Office of Policy -- I don't think that they're routinely participating, but there's -- the controlled substance staff may be involved. There are a number of different groups. The pregnancy group may be involved. It really depends on the product. But there isn't a standard team that we've used in every plan.

MS. ROBINSON: So can one expect then that when the risk management plan is submitted to the division that at the same time the division review is going on that it's submitted to the other interested parties?

DR. WILLY: Yes, hopefully.

DR. KWEDER: I'm Sandy Kweder from the Office of New Drugs. Good morning, everybody. I have a sense that you have actually a more specific question than that. Do you want to clarify it?

MS. ROBINSON: Actually I don't. It was just

from something I've seen over the last year in the pink sheets, just announcements that implied that other divisions would be reviewing the risk management plans, and it's really just a very open-ended question. No bad experiences.

DR. KWEDER: Okay. And I think I can highlight a little bit. One question, of course, is how do we decide who else gets involved. Mary captured it nicely. It really depends on what the focus of the plan is. And I will say that for any product -- that any RiskMAP that has a risk would be considered a restricted distribution component, the Office of Chief Counsel does get involved. That's become a standard.

If it has anything to do with children, we would have our own Office of Maternal and Pediatric Health involved. We might engage at the commissioner's level, the Office of Pediatric Therapeutics, depending on, you know, what the restriction was. For example, I can give you I think maybe a product that has more -- that may have

a program with a RiskMAP that focuses on a particular area of safety concern, but also has another safety concern that perhaps wouldn't warrant that level of involvement.

And let me give you an example. A good example is isotretinoin that's the focus of the risk management plan and restricted to distribution is really preventing pregnancy exposures. However, there is a lot of concern that patients and providers be educated about the potential for neuro-cognitive effects of the drug.

Now the Dermatology Division and the Pediatric and Maternal Child people with the Office of Safety and Epidemiology would be involved in most of it, but would certainly have some input from our Division of Psychiatry on how to make sure that any educational materials and advice were getting the right message across about potential adverse neuro-cognitive effects. So does that help you?

MS. ROBINSON: Yeah, that's perfect. That's perfect.

DR. KWEDER: Great.

MS. ROBINSON: Thank you very much.

DR. STROM: I would only add since I'm looking in your direction, I'm looking at my colleagues from the Office of Compliance that again for any particular drug where there are issues related to diversion or, you know, potential product that might be -- where patients might be looking to the Internet for the product, that we also involve that office as well as looking at the plan. So again it depends on the nature of the product and some of the issues and challenges that are raised in managing the risk of that particular product.

DR. SELIGMAN: Yes, sir.

MR. HEMSWORTH: George Hemsworth, (Indiscernible) Pharmaceuticals. I do have a very specific question. In the context of the original NDA, does the reviewing division expect to receive a risk assessment which may or may not lead to a RiskMAP, at the time of original submission of the NDA, or is that a post-

submission activity? And if it's post-submission, when would the division expect to receive it?

DR. SELIGMAN: Might as well. I mean I --

DR. KWEDER: Sure, I'll try. I think it depends on the -- it depends on the issue. We absolutely see applications that coming in right from the get-go clearly are going to require some kind of RiskMAP. And in those cases, we would expect to see that as part of the application. If a RiskMAP becomes -- if the need becomes apparent after a product's marketed, then we would expect to be communicating with the sponsor about a RiskMAP after it's marketed. It really depends on what point in time one identifies a risk that would require something specific in the way of trying to mitigate risk.

DR. SELIGMAN: The only thing that I would add to that is that, in Europe things are done differently than they are here in the United States. You know, at present the ICH, that's the International Conference on Harmonization, E2E document, you know, calls for doing

that kind of assessment in the context of pharmacovigilance planning and looking carefully at the kind of additional data that might -- or should be collected post-marketing based on such a risk assessment. So my sense, although I don't know this for a fact, is that that's occurring either more commonly or universally on the other side of the Atlantic. Yes, sir.

MR. HEMSWORTH: Just to follow up with the discussion and maintain the theme. Sandy, thanks for being here today. You know, our experience has been -- two things. One, our experience has been we've been successful in engaging the various review divisions at sort of a pre-NDA, even as early as the end of Phase II to start to have discussions on the need for risk assessment, risk management, risk minimization. So at the time of the NDA submission ultimately, all things being equal, both sides would be on the same page and the expectations would be there of what would be needed at the time of an NDA filing.

But just going back to the questions raised by my colleague from J&J, you know, more of a procedural -- when an NDA comes in, and it's been identified that NDA will have a risk management program, or risk management plan associated with it, how does that RMP -- how is that reviewed in association with the ongoing safety and efficacy review that's being done at the division level? Are they concurrent? Are they -- you know, it would seem that there would have to be some agreements reached at the division level on the benefit risk and the safety and efficacy before a more thorough evaluation, streamline approach to the proposed risk management would need to take place.

So how -- I guess my first question is how does that process work. And then secondly, are you seeing, as more and more drugs are requiring risk management plans and things are becoming more complicated, are you seeing that extending -- the need to extend your PDUFA action dates, your review dates?

DR. SELIGMAN: The answer to the first question is yes, they're generally concurrent. They generally move along at the same time. We are always, as you know, very sensitive to PDUFA goal dates. And to the degree we can, you know, be true to them, we try to be true to them. Are you aware of any circumstances where we've actually had to extend the goal date as the result of a risk management plan analysis? I don't believe so.

MR. HEMSWORTH: I'm not aware of one, no.

DR. SELIGMAN: So that in a sense answers the question, which is we tend to move them along in parallel.

DR. WILLY: Yeah, I would just like to add that we, our office, the risk management group, attends these meetings with the division, the pre-NDAs or into Phase II, and give our feedback as is needed. And we do like to encourage sponsors to bring in as much as data as you can and get started early rather than waiting till the end.

MR. HEMSWORTH: That's encouraging. I'm glad to see that you're plugging in earlier.

DR. WILLY: Very active, yeah.

MR. HEMSWORTH: Very good. Thanks a lot. Thank you.

DR. SELIGMAN: Absolutely. And why don't we take one final question?

MS. COHEN: This is Nadine Cohen from Biogen Idec. I just wanted to mention that we did work with the agency and the PDUFA date for natalizumab. Had to be delayed by three months in order to put in place everything that needed to get the RiskMAPs set up. So there has been that experience at least with the agency.

DR. SELIGMAN: Okay. Thank you. With that, I want to thank both of our speakers and all of you for the first session. One of the commenter's threw down an interesting gauntlet in terms of a goal for educating consumers, and their role in the area of risk management. And that's where we're going to start on the issues related to consumers starting at 10:15. Thank you.

(Break.)

(On the record - 10:15 a.m.)

DR. TRONTELL: I'd like to ask people to take their seats. We're going to be starting the first session in about a minute's time.

(Pause.)

DR. TRONTELL: Hello, and thank you all for keeping to time. I am Anne Trontell from the Agency for Healthcare Research and Quality. We're about to kick off a series of very important panel sessions directed around the different stakeholder groups that Mary Willy talked about in her presentation, whom we wish to engage in dialogue about the subject of RiskMAPs.

So I'm pleased to introduce our first panel. Representing the patient advocacy and consumer community. It's chaired by Terry Toigo, who's the director of FDA's Office of Special Health Issues. Terry.

MS. TOIGO: Thank you, Anne. Let me just pull up my -- okay, good morning, everyone. And thank you to our host from AHRQ and to the meeting organizers for

inviting me to chair this session.

My panel number one colleagues are here today to talk about some consumer and patient perspectives on RiskMAPs. And Dr. Seligman and others discussed the objectives for the meeting, and they're condensed on this slide. These objectives are to initiate constructive dialogue and information sharing, to share some key lessons learned, and to explore how tools being actively developed may improve the development of RiskMAPs.

Our panel will focus mostly on objectives number one and two. For lessons learned, we hope to hear from the panel on something about how we can apply experiences learned from consumer and patient discussions to future programs, how better to minimize risks while providing patient access and avoiding adverse unintended consequences, and how might consumers and patients best be engaged in meaningful and constructive partnerships and collaborations.

We'll start with our patients, Cheryl Bloom and

Ken Makowka, who will share some specific information. And then we'll hear from our consumer representatives. You'll see on your program that it has Bill Vaughn and Amy Allina, who will provide a general perspective. Unfortunately Amy called last night, and Amy is sick. But she did share with me her comments, which I was going to read to you this morning, but instead, since we have the director of our Office of Women's Health, and Amy is representing the women's health group, Kathleen Uhl has agreed to give Amy's comments.

But let me introduce our panelists. Bill Vaughn is currently the senior policy analyst in the Health Sector for Consumer's Union. And Consumer's Union is the non-profit independent publisher of Consumer's Reports. Starting in 1965, he worked for various members of the House of Representatives Ways and Means Committee and retired in 2001 as the Health Sub-Committee staff director for the Minority. Between 2003 and 2005, he was director of Government Relations for Families USA, a national

health advocacy organization. So he will certainly be able to represent the consumer perspective on the panel.

And Cheryl Bloom was diagnosed with MS in March of 2001, and she holds a Bachelor's degree in horticulture and owns her own landscape business in Eagle, Idaho. She is also a pilot, and Cheryl is a former moderator of the official on-line support forum for the National Multiple Sclerosis Society and is on the programs committee for the Idaho Division of the National Multiple Sclerosis Society. She's currently in a clinical trial for an MS drug, and she's testified before FDA Advisory Committee meetings.

Ken Makowka chairs the Fairfield County Multiple Myeloma Society in Wilton, Connecticut. And he was first -- he was misdiagnosed in 2000 with fatal plasmacytoma, but ultimately he had a stem cell transplant which has resulted in complete remission of his multiple myeloma. Ken started a security packaging company in 1984 and currently still successfully manages it. So that's the background of our consumer and patient panel. They have a

-- in addition to being patients and consumers, they have a lot of other things that they bring to the table.

So our format for each of the -- for each of our panelists will be to present for no longer than 15 minutes, and then we'll open the session for questions from the panelists to each other, and from the audience to the panelists.

And these are the questions that we ask our panelists to consider when they were preparing their comments. And I know from discussions with them that we've had prior to this session, these weren't the easiest questions for them to address. But nonetheless, they have tried to do that in their presentations, and we look forward to hearing from them. So we're going to start with somebody who offers not a narrow perspective, but we're going to start with the narrow, an MS drug, and then we'll move to the more broad perspective from the consumer groups. So Cheryl, we'll have you get started.

MS. BLOOM: Good morning, everyone. I think I

came a long way to be here. I'm not a professional speaker, so bear with me here. The RiskMAP and TOUCH stands for Tysabri Outreach Unlimited Commitment to Health. Protocol was the end result of the FDA hearings in March, 2006 for tracking potential cases of PML, progressive multifocal lugo-encephalopathy. That's the hardest word I'm going to pronounce today.

I have conducted an informal survey of multiple sclerosis patients to ascertain their experiences with the TOUCH protocol. While these patients seem to understand and agree with the purpose for tracking the potential adverse events, there are some who have experienced concern and confusion about the enrollment process, as well as problems with scheduling appointments for their infusions.

Some MS patients suffer from cognitive impairment caused by their disease and should not be further stressed with confusing enrollment process to obtain Tysabri. In addition, patients determined to need

Tysabri may have declining overall health since Tysabri is not considered a first line of defense drug for the treatment of MS. The RiskMAP for Tysabri requires that all neurologists, patients, pharmacies and infusion sites be certified.

I had planned to use slides for the TOUCH patient enrollment documents, but I found out that I cannot touch these slides.

The beginning of the process for the patient to become enrolled to receive Tysabri is the TOUCH patient prescriber enrollment form, the four-page document that is filled out in a neurologist's patient appointment, and which when filled out and signed, becomes the informed consent and prescription for Tysabri.

At the appointment, the neurologist explains the form to the patient, along with the risks, benefits of the drug, and of the procedures to infuse it. The neurologist gives the patient time to ask any questions and to fill out and sign the enrollment form. Then the neurologist

signs the form and faxes it to Biogen. Biogen now becomes the liaison for the final steps of the enrollment process.

Biogen will assign the patient identification number, ensure all the paperwork is filled out properly, ensure the patient has insurance coverage, identify and/or assign an infusion site if required, and notify the neurologist's office of any problems that need attention, and notify the infusion center that the patient has been approved for infusion. Once all these items have been completed, the patient has now been enrolled into the TOUCH system.

The patient enrollment number stays with the patient as long as the patient receives Tysabri. It is their unique identification number and is attached to all their paperwork, as well as to each vial of Tysabri they receive, no matter what type of pharmacy issues the drug.

Two types of pharmacies can dispense Tysabri, specialty pharmacies and central pharmacies. They both can order -- make sure I'm on the right slide here -- they

both can order on a just-in-time basis as the patient is scheduled to receive an infusion. However, a central pharmacy is allowed to order Tysabri without an enrollment number to dispense for unscheduled patients. When the unidentified vial is dispensed, a patient identification number is assigned to that vial for tracking purposes that's meeting the RiskMAP protocol for mandated controlled distribution of Tysabri.

TOUCH protocol requires that prior to each infusion, a mandatory pre-infusion checklist be completed by the infusion site staff. The checklist includes a notice of patient authorization or a notice of patient discontinuation for the tysabri infusion. If an authorization is not on file, the infusion procedure is stopped there.

After authorization is confirmed, four questions must be read aloud and vocally responded to by the patient. If the patient answers yes to any of these questions, the infusion site staff must call the patient's

neurologist prior to commencing the infusion for authorization to continue. If the staff member cannot reach the neurologist, then the infusion is rescheduled.

Once the infusion has been completed, the form is then signed by the infusion site staff member and faxed to Biogen. This form must be completed and faxed within 24 hours of the completion of the infusion or within 24 hours of cancellation of the infusion. If these steps are not followed, the infusion site could lose their certification. The notice of patient authorization is one of the reminder tools that the neurologist who sent after the patient has been on Tysabri for five months and every six months thereafter as long as the patient is receiving Tysabri.

The goals of the TOUCH protocol pre-infusion checklist are safety and tracking of PML and any other adverse events that may occur during the Tysabri infusion. Because Tysabri was re-released less than a year ago, the TOUCH protocol is a relatively new process. The reminder

tools that are in place haven't had much time for feedback with regard to their effectiveness.

I spoke with two infusion centers and several neurologists who seemed satisfied with the current system. The only reminder tool that I could get information on is the notification to the prescribing neurologist at the five-month point that his or her patient should be seen prior to their sixth infusion for re-authorization of the prescription. If there are other reminder tools in place for the TOUCH protocol, I was unable to gain access to them.

In the beginning, I stated that some MS patients have cognitive issues that are caused by this disease. I would like to address the issue of cognitive impairment and literacy of patients with regards to understanding the forms and information of the RiskMAP, as well as enrolling in the TOUCH protocol. The prescribing neurologist has an obligation to make sure that the patient is well informed and understands the procedures fully before leaving the

office, even if the patient has cognitive issues and is illiterate.

Questions. How do these issues get resolved? Are these issues for which the infusion site personnel should be responsible, or are they the responsibility of the treating neurologist? Cognitive decline should be noted as it could be a symptom of PML, but not just one of the symptoms. Illiteracy. This issue is trickier. Due diligence on the part of a treating physician is part and parcel of his care to his patient.

Some of the questions that patients have asked. Number one, what is the real purpose of the TOUCH protocol. To my knowledge, no one at MS Active Source, Biogen, was able to answer this question. I have responded that it's purpose is to minimize the risk of PML.

Number two, why can't MS Active Source help me with insurance-related questions, i.e., act as a liaison to assist with insurance approval problems? Several

patients have complained about the difficulty in obtaining accurate insurance coverage data, i.e., out-of-pocket expenses, reimbursement information, what part of the plan covers the infusions. They get bounced around between the doctor's office, the infusion center, and the insurance company. Some of them have been playing the game for over nine months.

Number three, can I switch infusion sites when I go on extended vacations? No one has been able or willing to answer this question for several patients.

Number four, how many days can I slide my infusion appointment? One week either slide for my prior infusion? The recommended time between infusions is four weeks. Is it possible to go three weeks or five weeks?

Other topics for discussion. Number one, continuity of care at the infusion sites. Do the patients have the same infusion staff person each time they are infused? This is important for safety goals, PML observation, cognitive changes. One patient I interviewed

said the pre-infusion checklist was not even covered before her infusion. The infusion site staff didn't even know what it was.

Number two, could the drug be available outside the system? If the drug is tracked the way it is supposed to be, one vial, one patient, I think it's highly unlikely that Tysabri would end up being used off label or available on the Internet. But I don't think that's my area of expertise.

Number three, infusion sites not receiving the drug in time for infusion appointments. This has been happening more and more frequently. Patients are scheduled well in advance, and the drug is shipped overnight. Why is this happening? It places undue hardship on MS patients, especially those in rural areas who have to travel great distances only to find they have to be rescheduled.

Number four, also there have been several incidents of the drug being mixed improperly with D5W

instead of saline, which means they have to reorder the drug, reschedule the patient, and infuse them again.

Recommendations. Number one, mandatory recurrent or periodic retraining of infusion site personnel and neurologists. Number two, survey of patients after six months of infusions to check their opinions of the infusion site experience. Number three; make it very clear during the neurologist training process who initiates the TOUCH enrollment process for the patient. Number four; solve the drug delivery process to the infusion sites.

Thank you for allowing me the opportunity to speak to you about the RiskMAP and TOUCH protocol for tysabri and giving patients a voice.

MS. TOIGO: Thank you, Cheryl. We're going to do -- we'll do questions at the end. Ken, are you ready?

MR. MAKOWKA: Yeah.

MS. TOIGO: Okay.

MR. MAKOWKA: Hi. My name's Ken Makowka. I'm

from Wilton, Connecticut. I'm a seven-year survivor of multiple myeloma, which is pretty good because when I was diagnosed, they told me I had the life span of 18 to 36 months. So I'm over the curb.

There's 750,000 cases worldwide of multiple myeloma. Just last week, Don Herbert, the Wizard, died of multiple myeloma. Ann Landers died of multiple myeloma. Peter Boyle of "Raymond" died of multiple myeloma. Roy Scheider, the actor from "Jaws," has multiple myeloma. It's very rare disease, but everybody knows someone or has heard of it indirectly. It's not melanoma which most people think, oh, you can get that fixed.

There's 16,000 cases that are known to the doctors every year. It's almost equal, 54 percent male, 46 percent female. A very ironic statistic is that 9.5 cases per 100,000 are Afro-Americans versus only 4.1 cases in Caucasians, which brings up a point we'll discuss later. There's 50,000 survivors in the U.S. as of 2005. Ninety-nine percent of the patients are over 40, 50

percent are over 71. And this is almost consistent in diagnosis also. But unfortunately the trend is towards younger patients, which does have an impact on some of the drugs that are being used.

Myeloma's a cancer of the plasma cells. It's the number two blood cancer behind lymphoma. It's incurable but treatable. There are known survivors of 17 to 19 years. Unfortunately based on the time of diagnosis, if it's too late, that's where the real low numbers come in. People die within six months in a lot of cases.

A few years back right after the (indiscernible) project was finished, I was at a seminar, a workshop, on myeloma. And then my colleague made a rather telling statement. He said the bad news is that you have cancer, but the good news is that you have myeloma. The reason for that being that bone marrow is where it happens, and they can get really fast results on a drug on myeloma patients. And henceforth, then if it does work, if it

goes through the trials, they can apply for applications and other cancers.

I was kind of surprised when I found this out two weeks ago. There's 316 trials involving myeloma. A lot of these are Phase I, a lot of them are combination drugs, some of them are even old line drugs. And that brings up another consideration as far as RiskMAPs are concerned. When they're doing a cocktail, how is that handled? No one seemed to really have an answer for that.

As was mentioned earlier today, there's -- within the last two years, there have been a number of drugs for myeloma which are the first drugs in about 15 years that were specifically approved. Velcade from Millennium, that's an injectable drug. Revlimid and Thalidomide which are from Celgene, which were mentioned earlier are part of the RiskMAP program.

Something else that was hit upon a little bit earlier was the bisphosphonates in osteo-necrosis of the jaw. And as best I can tell, Aredia and Zometa are not

RiskMAP drugs. And three years ago, I was involved in a survey with people who were taking bisphosphonates for over long periods of time were getting degeneration of the jaw. And to my knowledge, Novartis hasn't really identified the problem or admitted to it in my estimation, and I'm at the low end of the food chain here. I'm a patient. And I stopped taking it for that very reason because it was in my case unjustified. I didn't have any active bone involvement, so I really didn't need to have a bisphosphonate. And I do get a bone scan every year, and I'm above age group. So I saved the insurance company about $1800 a month.

Of my investigation, was a little bit worse than what poor Cheryl went through. Of the 12 patients that I contacted that had been on Revlimid or thalidomide from Celgene, none of them knew what the word RiskMAP meant. In reading a lot of -- doing a lot of research on the programs themselves, yeah, they had, what shall we say, the protocol of going through it, but they didn't exactly

know why. And again, go back -- most of these people were older, so they weren't necessarily assignable to the pregnancy risk that thalidomide is noted for. None of them knew anything about that risk associated with Revlimid.

One of the patients is an internist. And he had heard of RiskMAPs, but it was not for -- and he's on thalidomide, but he didn't know that they were one the list. And he did -- because he had prescribed Lotronex -- is that how you say it? I contacted the International Myeloma Foundation, which is the largest worldwide organization, and their help line with three people, none of them ever heard of RiskMAPs. But they know a lot about thalidomide. They know a lot of Revlimid.

Of the four physicians that I contacted, two were internists, and they were the ones that had the experience with Lotronex. The oncologist, which one is a noted worldwide authority, he sent me back an e-mail saying never heard of it. Let me know what you find out.

But one of the internist came up with a rather onerous statement saying he could see the need for the control, but he found the system to be very onerous. And brings up my investigation of it -- okay, just how it involves the myeloma drugs.

At the time last week, I couldn't confirm that Revlimid or thalidomide were in the program. I found that out this morning. And that was after I called Celgene. They didn't know anything about it. And I played the devil's advocate. I wasn't going to talk to the Compliance people. I talked to the help line and the patient assistant.

But I did have some of the patients in our support group, we went on a conference call and we called in. They did their registration, and they did the four auto questions. The biggest thing that surprised me was it wasn't the pregnancy involvement or potential. It was the fact that did you share your drug with anyone else in the last month, which seems to be risk management on the

pharmacy count.

But as stated earlier, in order to be eligible for Revlimid or thalidomide, you had to have both the patient and usually the physicians already been in it. Since both of these drugs were in trials for so many years, and since I live in the northeast, the oncologists involved were in the trials, so they were pre-registered. So it's not a big deal. A few of our patients that are in the support group have local oncologists, and I guess because thalidomide's been around for a while, they do prescribe that. Surprisingly, the local physicians or even the local oncologists don't know enough about Revlimid, so they haven't registered for that program. Is that doing the patient's best? I don't know.

And then in order to pick up the script, the pharmacy has to be registered. There is the monthly call-in as I mentioned. There are the auto-questions, which seem to vary by male versus female. But since they went through so fast, I wasn't really sure. And then something

that I'm not exactly sure of why, and no one could explain it to me, but once the script is authorized, you have seven days to pick it up, or you go through the process again.

So how does it impact myeloma as far as RiskMAPs are concerned? The population involved, the patient group, doesn't know the first thing about it. Unfortunately neither did the doctors, the nurse practitioners, the nurses, and as I said, the patient himself, meaning me.

And then this did come up by talking to some of the doctors, and the patients that were worried if the word onerous is being used, is that going to impact upon what the doctor is going to prescribe in the future. If there's 316 new trials of combinations, how many of those new drugs are going to go into RiskMAP? And I'm here to learn really because I have to report back to all these doctors now. But it is amazing what precipitates it. So that's something for us to all learn, right? Thank you.

MS. TOIGO: Thank you, Ken. You raised some interesting comments that we'll save for the question period. Dr. Uhl, maybe you'll come up now and do Amy's comments on the -- this is from a women's health perspective, our consumer perspective. So pretend Cook doesn't have her uniform on, and she looks like Amy Allina.

MS. UHL: Oh, that would be fun. Amy's younger than me. I'll take that. I'm Kathleen Uhl and the director for Office of Women's Health at FDA. And Amy Allina is with the National Women's Health Network. And that's a group that the agency works fairly closely with. They are a consumer health group. They are located in Washington, D.C. Our office and Terry's office has tremendous amount of interaction with this group. But she has sent her comments, and I'm just going to read them to you.

She basically has three comments with some explanations. So as I get to each one, I'll just let you

know. So her first comment is "med guides are valuable, and the FDA should make more use of them." So she says here "when women have accurate and balanced information about drugs, they can and do make good decisions about what products they want to use. Unfortunately many aren't given that opportunity because the information most readily available to women and clinicians all too often comes from drug company marketing departments whose aim is to sell a product.

RiskMAPs can play a critical role in providing women and clinicians serving women with the information we need. The risk communication that women need is not just about adverse events and side effects, but also includes an accurate and not over-inflated presentation of benefits so that it's possible to weigh risks against a good understanding of the potential benefit. Creating med guides for more drugs, and National Women's Health Network believes that there should be med guides for all drugs, would help consumers to play a more active role in

managing risk." So that's comment number one.

Her second comment is that "education tools will not be enough in every case, and the FDA must be able and willing to establish and enforce additional protections, such as restricted distribution systems." So within that comment, her additional ongoing comments are "initial restrictions on isotretinoin, for example, did not provide consumers with adequate protection against the risks of the drug. This is an example of particular concern to the National Women's Health Network because isotretinoin's teratogenicity imposes a specific burden on women taking it, who must observe a high level of care with contraception, or face the possibility of the difficult decisions that come with an exposed pregnancy.

Women with the most severe acne speak to the life-changing benefits that this drug offers. But there have also been high levels of use of the drug by patients with much less severe conditions. And with the broader use of the drug comes broader exposure to its serious

risks. There is more likely to be a need for a restricted distribution system when a manufacturer is heavily promoting the drug through campaigns targeting prescribers and patients as has been the case with isotretinoin."

Her final comment here is "the FDA needs expanded authority and resources for risk management, including new tools for restricting and monitoring direct-to-consumer advertising and promotion of drugs to prescribers."

So as her first two points demonstrate, "risk management efforts are frequently undermined by drug promotion campaigns. The FDA does not have enough resources available for monitoring drug promotion to clinicians and consumers to ensure that drug marketing campaigns do not cross the line into promoting use of drugs by patients for whom the proven benefits do not outweigh the risks.

Moreover, the agency also needs explicit, additional authority to restrict the advertising and

promotion of new drugs until the risks have been well enough characterized to understand which promotions -- which populations can safely use them, under which circumstances.

The information collected in a clinical trial of limited size and duration conducted in a narrowly defined population is frequently not adequate to support a full understanding of the risks that will emerge when the drug is on the market and being promoted broadly. The National Women's Health Network strongly supports proposals to give the agency the authority to delay approval of direct to consumer advertising for new drugs until potential serious side effects are better understood and to help consumers understand the limited knowledge base that exists for newly approved drugs." So that's Amy's comments.

MS. TOIGO: Thank you.

MS. UHL: Sure.

MS. TOIGO: And Bill is going to give us the consumer perspective. And you have handouts, right? And

did people get them?

MR. VAUGHN: I hope most people got them.

MS. TOIGO: In the back, okay.

MR. VAUGHN: I brought about 150, and that's probably a little shy, but I put an e-mail at the bottom. And if anybody wants an electronic copy, I'd be happy to send them for what they're worth.

Consumer's Union, we're the publisher of Consumer Reports and don't just test toasters and things. But try to help people with safe and effective drugs. And we have a free service on our CR for Consumer Report's bestbuydrugs.org, which uses some of the work of AHRQ to help people find the most effective, safest drugs in the category. We put price beside it and kind of make a, you know, recommended best buy. And so we thank AHRQ for that help in that effort.

We've been working for a couple of years on a campaign for FDA -- I won't use the word reform, but change legislation that is moving through the Congress and

is what part of the handout is about. And the new bill covers pretty much everything Dr. Willy was talking about. My handout concentrates on the RiskMAP parts. And I'd like to talk a bit about this because when I said yes to coming here today, I thought some of the hundreds of activists we had on this campaign to get this legislation passed would have had had personal RiskMAP experience. They did not. And so I'm not sure how much else I add today.

But the legislation that is referred to in the handout passed the Senate in early May, 93 to 1. Thank you, China. An amendment was offered by Senator Durbin that had six parts, three on human food safety and three on pet food safety. Any guess which three appear first in the amendment? Wouldn't want to vote against my dog or cat, so it passed easily. It cleared the Energy and Commerce Committee Thursday by a vote of 43 to zero, again strong support, and we expect it on the floor the week of July 9th. And as you can see from the handout, it's

pretty much what we're talking about here. It's sort of Congress catching up with what FDA is trying to do. Whether it's working well or not, it's what the FDA was trying to do in RiskMAP.

And in terms of writing the reg on this one, when you look at it, it ought to be an easy reg project. You take your March, '05 guidance and put it in the Federal Register. There may be a chance for small technical changes over the next couple of weeks, but as you can see, the bills -- the two bills are very similar. A lot of emphasis in the debate on burden on doctors, a couple of doctors on the committees. Burden on rural America. The Senate uses the term frontier, which I bet is what Eagle, Idaho feels like in December, huh? A little difficult.

MS. BLOOM: Hot and cold running water.

MR. VAUGHN: Hot and cold running water. That's good. But trying to make sure that patients in rural and frontier areas are able to get help.

And basically what I think this section of the legislation does is take away the legal cloud of whether the FDA can insist on a RiskMAP. And you don't have to go begging for it or negotiate too long on it. And maybe this gets the General Counsel's office out of the cycle of having to run these things. And as I say, Consumer's Union supports this effort.

I am fortunate nobody in my family has ever had one of these illnesses and had to go through this kind of medicine. So I don't want to feel or sound unempathetic, but I am concerned about the very intense lobbying that did occur around the RiskMAP sections of the bill by those who want to -- whatever -- perhaps sell more medicines or get money from drug companies and who work in think-tanks and spend their time writing editorials in the Wall Street Journal that a RiskMAP is an insult to doctors, to their professional competence in being asked to ensure safety is interfering with the practice of medicine. That basically is what has been said.

And when you hear that kind of comment, just myself as a consumer, it's why I think I'm against limits on malpractice suits. That there is a lot of malpractice out there, and that the Jekyll and Frankenstein School of Medicine is not a good one, and that complying with some FDA guidance is good and is acceptable.

If last night three 727's carrying about 497 people crashed, that would be a banner headline, wouldn't it? And every single day in America, if you use Dr. Strom's numbers, that's the number of people who are dying in our healthcare system because of mistakes and errors. If that were to happen, first of all, not many of us would fly, would we? Second, we would demand a lot more from the airplane manufacturers and the pilots. I don't know what goes in the cockpit. You're a flyer. But do you think pilots say to each other going over the checklist is degrading and insulting to my professionalism? I've been flying jets from Viet Nam, and let's just wing it? Let's skip the checklist? I hope not. I hope not. But that's

really the tone of what you hear in some of this attack on RiskMAP. And as a consumer, it makes me grumpy.

Our healthcare system is broken, and we need more full-proof systems to reduce the level of human error. In addition to the deaths that Dr. Strom talks about, there's apparently one medication error per day per hospital stay per patient. On an average, adults get half, half of the services which they could use and which would be good for them. And there was data last week on a Medicare Managed Care plan. One of them was doing eye pressure checks on its diabetic enrollees 8 percent of the time. For this, we the taxpayers pay them 800 or $900 a month? Nice work if you can get it, but I'm tired of paying for that kind of quality.

And it's sort of everybody's fault. We patients have failed. As Cheryl points out, there is severe illiteracy problems. There's a Dr. Davis in the annals of internal medicine who cited half the people, half the people misinterpreted one of five labels. Those with

sixth grade literacy, 71 percent could read aloud take two tablets by mouth twice daily, but only 35 percent of those correctly took four pills from the bottle.

And so for some of our most vulnerable, when you're really sick, the third of Medicare disabled who are there because they're mentally ill, the four or five million with early dementia, understanding package inserts, med guides and so forth is sort of a, you know, forget about it. We've got to have better systems.

Now most of us are above that level of literacy. Thank gosh. And that's why we got to keep working on the med guides. FDA's been working on what literature to apply for 40 years now. And Congress in this new bill is going to ask you to do it again. Report in a year on risk management, and you know, I'm glad we got computers, and you can download some stuff. But it's important, it's important that we explain these risks so much better.

And we're not an agency -- consumers not an easy crowd to keep safe. I mean 21 percent of us are still

smoking for gosh sakes. And we're talking about RiskMAP. You know, if one pill helps, two ought to be better, right? Thank gosh for all the motorcycle drivers who don't wear a helmet. They keep the organ banks open. So it's tough dealing with us.

But the doctors have failed. I don't think it's their fault. But 15 years ago, I think I read the first time, if a doctor read two peer reviewed articles from a medical journal every night, and at the end of year, he'd only be 750 years behind. I bet you by now he'd be, I don't know, 1200 years behind with the flow of information. And just for my own personal doctor, who I love. I just bet he hasn't read to the end of the desk guide on every pill he prescribes. It's just too much.

And, you know, we're on our third effort on Accutane, and the second RiskMAP, I guess the number of pregnancies actually went up. So there's failure there. As for the companies, their fiduciary duties is to sell more pills, you know, and they get hundreds and millions

of dollars of fines for pushing off label. But somehow you think it's still going on a bit. Look at how EPO has been pushed over the FDA prescribing levels. Or Vioxx, pushed way beyond its natural audience.

And as a consumer group, we feel bad that the bills moving through the Congress have deleted any temporary moratorium on direct to consumer advertising. There's some improvements in trying to limit bad ads or ads that don't share adverse events adequately, but it's pretty weak stuff.

And I just would say on the company side, I've seen some things. They may not have been in RiskMAPs, but for a company to manage, gee, asking what are your other medications, it makes sense. You need to know interactions. But that's a fine line to starting to market. Why don't you switch to all our products. And I would hope that never ever happens and should be forbidden or prevented in some way.

But given all these faults of all the key

players, we support your efforts at RiskMAP, but hope that the evaluations will keep them flexible in trying new approaches and getting rid of the nuisance stuff so that we really pay attention to what's important in these things.

Speaking of airline safety, could somebody please stop telling me how to buckle by seatbelt? You know, I blush for the poor flight attendants because if you could get through TSA, you've got to know how to buckle seatbelts. And then maybe some of this -- and, you know, maybe the fifth time you fill a prescription, don't do this part because you sort of tune out the important stuff. And if that mask ever comes down, you know -- I know a Jet Blue flight attendant said stop screaming and put it on, you know. Once I quit screaming -- that's what I want to pay attention to is the more important stuff and stop tuning out -- I think Dr. Strom referred to it as warning fatigue. Warning fatigue. And that's a big danger I think in some of what you go through on these

things. And what we really need is foolproof systems. And RiskMAPs are an effort at systems, a step forward, not perfect, but systems we need to keep building on.

And what I mean is Consumer's Union has a campaign. I think we're about to win some legislation. For three years now, the big SUV's, the really big ones, terrible rearview -- about two children a week die and so often it's a parent or grandparent backs up in a driveway, and like 20 or 30 kids a week. Oh, Detroit. Well, I got to educate parents not to back up over their kids, you know. That was the answer. There's a little device that I think we're about to get legislated and poor people won't thank us. It'll drive car prices up 30, 40 bucks. Little device that will be like a little radar screen. And if you -- and if there's something right behind you, a tricycle or a kid, let, you know, big sirens go off. And it will be very hard to back up over your kid. That's the system. That's foolproof. That's better than telling a parent not to kill their kid because people make mistakes.

And that's what we need in these systems.

And one chance would be E-prescribing. About 3 percent of doctors are doing it. We know how to do it. The systems are there. The estimates are that by 2015, we'll be up to like a third, and yet we know we can reduce errors. We could catch some of these things that shouldn't happen, contra-indicated drugs. And why not as a society just say do it? If there was a new radar system in an airplane, you wouldn't say, well, that's a hassle to learn how to do it, pilots do it, right? I mean how do we get that kind of mentality of, I don't know if safety first is the word, but that safety is worth the inconvenience? And that's something that doesn't seem to be here.

And then the same thing applies for electronic health records in general. If we had a national system -- the VA has it. That's how they came from being kind of -- to being rated number one because they know what their patients are doing and when they've done it. And why

can't we as a nation say by a date certain, we're going to do this?

And understanding a drug's true long-term benefit and safety would come much easier with a new provision in this bill that's passing, which is huge epidemiological databases available for active work, not passive work. The Senate says a goal of 100 million medical records available to the FDA by July, 2012. The House version is vague on the number, but the same concept of really -- and this comes from your former commissioner, Dr. McClellan, saying if we'd had a large database, we could have picked up Vioxx maybe in three months and not three or four years.

How about pay for performance? Everybody in Congress yapping about pay for performance, and we're moving there. That if you didn't participate or cooperate well in a RiskMAP, that gets into that formula somehow. I guess Dr. Metz is here, and your study of Lotronex, 87 percent compliance is the one I read. If that's dated,

let me know. But, yeah, in my high school, that was a B. It wasn't even a B plus. Eighty seven percent. What happened -- where were the other 13 percent of the doctors? Should that maybe fit into a pay for performance? I bet that'd get their attention. I bet we'd get a lot closer to a hundred.

And then also in his paper, he talked about doctors who were non-participants in the program. Seventy-five percent compliance after three letters, 25 percent enrolled in the program, 50 percent quit prescribing. What happened to the other 25 percent and where are they? Why aren't we getting closer to zero tolerance on errors like aviation does?

So we need systems that are flexible. Airbags are classic. They did kill some people. Babies, young people, small people have died in airbags. They have been trying to redesign them. They're weakening the passenger side ones. Kids are in the back seat now. They've been flexible to try to increase the benefit cost ratio of that

kind of system.

So we all make mistakes, patients, doctors, companies. And we do need better systems in place to catch those mistakes as soon as possible. And I think really I'm just saying what Dr. Strom said. This is an imperfect system, but I'm sure glad we're trying, and let's try to keep making it better. Thank you.

MS. TOIGO: Thank you, Bill. We'll now open it to questions. I think we heard certainly from Cheryl that there are concerns about the programs related to continuity of care. She had some comments about periodic retraining of people at infusion sites serving people after -- patients after six months. From Ken, we heard about onerous programs that might prevent a prescriber from prescribing. We also heard concerns about educating the physician community. And from Amy, we heard about that all drugs need RiskMAPs, and we heard some concerns about the influence of direct consumer advertising. And then from Bill, he expressed concerns about literacy,

restated Dr. Strom's discussion about warning fatigue, and then encouraged us to be flexible in our programs and evaluation.

And I think clearly whether you're in Idaho or whether you are in Connecticut, or whether you're perhaps somebody answering a consumer line at a company, you clearly know what the programs are, but nobody knows the word RiskMAP outside of this regulatory or the Washington community. So I think some of the questions that our panelists, when they actually surveyed their groups, using that term RiskMAP, people aren't familiar with it. And they also might not really be familiar with what the purpose of some of these programs are.

So with that, that's my take on some of our panelists' comments. But I'd like to hear if there are questions from our audience for our panel members. How about questions from our panel members for each other? David has a question.

MR. KAPLAN: I'm David Kaplan. I'm I guess a

patient advocate. I was involved in the Tysabri re-approval of the Advisory Committee hearing in March of 2006, so I can speak to that. I know a lot of MS patients. I'll make a couple of points if I may and ask a couple of questions.

When Tysabri was first re-approved, I had occasion to read FDA's med guide I think it's called. And I was distressed to see that it really only discussed the risks of the drug and really nothing about the benefits. And I was told that there was a process that was being undertaken to try and make these medication guides more balanced. I think that really makes sense to me as being a goal. I hope that's been done. I haven't looked at it recently.

But with Tysabri, I've found that this very rare, what appears to be a drug interaction between other immuno-modulatory drugs are immuno-suppressants causing PML scared a lot of patients from considering the drug when they really should. And really poisoned a lot of the

neurologists from giving full consideration to the drug. So with anything in life, it seems to me that there's some risk and there's some benefit. And there has to be an assessment made as to what those are for the particular patient under their particular circumstances.

And I'm just concerned that in the case I'm familiar with that there may have been a little too much in what direction than the other, and a lack of adequate balanced information made available to both patients and neurologists.

MS. TOIGO: Cheryl, do you want to address that, and then somebody maybe from our Drug Safety office wants to also talk about that. And actually the comment, David, that you made about risks and benefits, I've neglected to include, but that was also in Amy's -- Dr. Uhl - Amy's presentation on including information for patients on benefits as well.

MS. BLOOM: During my survey, that issue was brought up, David, about patients being afraid to take the

drug because of the literature presented to them both by their neurologist and from competing drug companies. One case in particular from a neurologist in my hometown was handing out PML literature when their patients came in and asked specifically about Tysabri. He was handing them PML literature on a competing drug company's letterhead instead of giving them information about Tysabri. So yes, scare tactics were out there, and it's unfortunate.

So how do you get around that, you know, educating the neurologist? And that's the drug reps' job. And I think the longer the drug's on the market, and no case is a PML or any advertised adverse events are presented is going to help.

And it's patients talking to other patients. The on-line support groups are a big help, but it's educating the community, and so that's the big thing, you know. But it's also the neurologist. They're afraid of lawsuits. I've had four of the neurologists that I spoke to say not on my watch. I won't prescribe this drug

because I don't want to get sued.

MR. KAPLAN: Well, I wonder when MS patients might be suing the neurologist because they're prescribing drugs which are half as effective as the most effective one rather than being concerned about the risk of -- I mean PML, as of May 23rd, and maybe somebody from Biogen Idec can update that for the last few weeks, there's not been a single case of PML from Tysabri.

MS. BLOOM: Well, the recent New England Journal of Medicine article I think addresses that, which is being published, what, this week? So you know, its education. It's getting the word out, you know, and that's exactly it, so I don't know.

MS. TOIGO: I don't know if Dr. Willy or anyone else wanted to address the comment about risk benefit information that he raised?

DR. ULE: Well, that's a difficult issue. I think we are very aware of trying to make sure that patients and physicians are aware of the risks and the

benefits. Oftentimes we see a lot of material that's prepared for the patient to see. Some of that can be overwhelming, and what they look at may be focused more on the negative part and not so much the positive part.

There was just I think last week, two weeks ago, a public meeting about medication guides and how they might be improved. Unfortunately I didn't attend, but I think there was a lot of feedback provided on that whole issue, and it's a process that we're continuing to look at, hopefully improving on. And I'm sorry. That's about all I can provide you.

MR. KAPLAN: I appreciate that. I've just invited somebody from the agency to look at the med guide for Tysabri because when I last saw it, I don't think there was a single word about the benefits. It was really -- it could have been called risk disclosure, but it was not a medication guide. Thank you.

MS. BLACKWELL: I'm Mary Blackwell. And I actually have a foot in several camps. I'm an MS patient.

I've been on Tysabri for seven infusions now. And I'm also a physician, although I do move in intensive care, so I'm not evenly remotely related to the MS world.

But I think I would reiterate David's point that the med guide basically is a risk information guide. It has no information at all about the good things that Tysabri can do for you. And I mean that's up to the doctor to provide you, or you to seek out yourself. The medication guide as it is currently put out has absolutely no information about benefit. It only has information about risk. You can die, you can die, you can die, you can die. Every month you're supposed to read that. And, you know, I think that's ludicrous. And every patient I see come on MS World, you know, saying my doctor has suggested Tysabri says I'm afraid. And, you know, maybe they should be afraid.

But, you know, sometimes it's like, you know, I tell people I was a lot more afraid of what was happening to my life before I went on Tysabri. But then as a

physician, I know a lot about how doctors think, and they are risk adverse, and they are adverse to cumbersome procedures.

And the other thing that I see from a lot of patients on the various Internet support groups is my doctor isn't prescribing Tysabri. And I think that that's a horrible thing. I mean that the access to this medication that is way more than twice as effective as anything else out there is being limited that way. My doctor's not prescribing because he's afraid and because it's too much trouble, although that's seldom said. So you know, I think it's really, you know -- there's a lot of work to be done. And I tell you I've been ashamed for my profession in my experience listening to other patients.

MS. TOIGO: Well, I think we've heard comments from Cheryl and David and you, and certainly we'll be considering those as we move forward. Are there other comments?

I have one for the group to think about. You talked about literacy, and Bill, you talked about it, and Ken talked about it. But when -- have you heard from patients about how they can understand the information that's being given to them? I mean is that -- you know, you're just generally raising it as a concern or have you heard some specific things from patients that -- I mean other than Bill's comment about, you know, if the mask falls down, put it on. Has there been any other specifics that you've heard that we could learn from when we're developing these programs?

MR. MAKOWKA: As far as the myeloma community, everybody goes along with the doctor because the doctor is playing with their life. It's a fatal disease. I don't know enough about MS. I'm very selfish because I have myeloma. And they keep trying different things because the efficacy doesn't last very long.

Now one of the things that surprises me is that most people stop taking thalidomide, not that it doesn't

work so much as the neuropathy problems that it causes. And it becomes so severe with the hands and the feet that it isn't worth that risk. But that's not a known risk that they're really talking about as far as sharing the drug or the impact on a pregnancy.

I don't know that that's been identified, but -- and that's like the test that they recently did up at Mayo. There was a trial with dexamethasone and Revlimid, and they were getting not a high incidence, but that's the one in a thousand becomes one in a hundred of DVT. So they found out by throwing aspirin on a daily basis, it works much better and it eliminated the risk, but I follow that. There's a lot of doctors that Bill mentioned that are 1200 years behind.

MS. TOIGO: You talked about outside the program. Do you have a feel for how often that happens and why specifically people are getting access to the drugs outside of these programs? Is it just a cost issue? Is it because it's onerous? Or did you get any feedback

from the people you surveyed about --

MR. MAKOWKA: Oh, that was very limited. Fairfield County is the wealthiest county in the United States. So they're not shopping for it out of Mexico or on-line. On the message board, yes, there's a lot of people who are looking for it because of the cost.

I'm confused because (a), I'm not on any maintenance drugs, but (b), a lot of the people that -- before thalidomide was given authorization as an improved drug for myeloma, a lot of doctors who weren't involved in trials were using it as an orphan drug status. And then the people had to pay for it. And the insurance companies, since it wasn't approved by the FDA, didn't pay for it. And it's a very, very expensive drug which becomes more and more expensive. And now when Revlimid was approved, a lot of trials were canceled, and these people were given the rest of the month's supply and said, you know, go fish.

And in a way -- a couple of them did say they

went back to the doctor and said I have to find a more economical alternative regardless of what they were currently doing. The good news is there's a lot of drugs currently. The bad news is a lot of them aren't approved. And people don't really understand what that means. Myeloma's involved in a lot of trials, so the doctors try to put the people into trials.

MS. TOIGO: Okay. Cheryl, you talked about periodic retraining for infusion site staff. Can you tell us a little bit more about what you were thinking about, or what problem you were trying to overcome by periodic retraining?

MS. BLOOM: There seemed -- from the patients that I interviewed, there seems to be I think, as someone put it, warning fatigue. Or as in the aviation community, we put it repetition. You become immune to what's going on. You don't hear the questions anymore. You kind of, you know -- you just repeat the motions. And people don't understand the question, you know, what does TOUCH mean,

what does the protocol mean. So if you don't understand what the process is, you don't know what to look for.

So the infusion sites staff needs to be trained on a periodic basis to know what they're looking for. And so this, you know, one time certification, I think that they need to have periodic updates so they know what they're looking for PML, for adverse events. And not just PML, but other adverse events.

And when I had one of these patients say nobody even went over the checklist with me, that infusion site should be de-certified now. And, you know, things like that. And then go over the protocol periodically. And then the neurologist as well, recurrent, you know, continuing education on what the protocol's all about, why is it there.

MS. TOIGO: Okay. Any other questions from our audience? Well, then I get extra credit for letting people finish early and get a longer lunch, unless Ann's going to use these 10 minutes.

MS. TRONTELL: No. I would, as we've told you, just give you some advice on exiting the building. You'll need to use your card again to scan out of the building. You can retain it and use it to come back. And you should have a facility -- there's other people around and information desk if you have questions.

It's my understanding that the gates for the parking lot will go up at lunchtime and go down after lunch, so you don't have to worry about paying twice if you choose to drive to get to your lunch. So let me thank you for your participation so far.

We'll be starting back at 1 o'clock with a panel looking at physicians and providers' perspective of RiskMAP programs. So do your best to be back on time.

(Luncheon recess.)

(On the record - 1:00 p.m.)

MS. TRONTELL: As people would take their seats, I can give you some information about follow-up to the meeting. I'm very pleased to tell you that all the

speakers so far have agreed to share their slides, so we anticipate being able to post those on the Internet site that you've seen before by the end of this week. And that ideally within a few weeks after that, we'll have a high level summary of the meeting. It may take a few more weeks past that for the transcript to be available, but since I know we had a number of people who were unable to be accommodated in our space or to make this meeting in the midst of summer, I'm pleased that we'll be able to share it to those who were unable to be here in person.

And just another reminder and request, when you do come forward to the microphone to ask a question or offer a comment, please do state your name each time that you do that so we credit you with what you've had to say.

Just to let you know this afternoon kicks off two sessions. We'll again be hearing from two important stakeholder groups. As I think we've all heard this morning, we have a complex, fractionated, and maybe sometimes fractious healthcare system where we all think

each component should be doing more. So some of our exploration of the system is to talk to each of those components. So we'll be hearing from first the providers and payers perspective. And then from the pharmacists and distributors of pharmaceutical products.

So let me introduce Panel 2 that's chaired by Dr. David Meyers of AHRQ. He is the acting deputy director of the Center for Primary Care Prevention and Clinical Partnerships, also known as a CP3. And as important as that is, I think Dr. Meyers is pleased to consider himself a family doc and has a panel of other providers to talk, as well as insurers, about how this all can work.

DR. MEYERS: Thanks, Anne, and welcome everybody again to AHRQ and to our second panel on the providers and payers perspectives.

As we've talked about already today, the meeting is really focused on bringing many different perspectives to this problem and working collectively to solve it.

Right now we're going to step back and hear from two groups, people representing the payer community, and people representing the prescribing community.

Here's our agenda for the next three hours, and this is a long sessions, and so this is your roadmap. We're going to do a very short introduction of all our speakers, and then we're going to start with the perspective from the largest, from a large payer perspective. And then we're going to use a segway of two large systems, but also hearing how they work with their providers, and especially about the topic of clinical decision support and computerized provider order entry.

And this is sort of a little tangential bubble around our larger focus of the meeting. As one of those tools that may be useful as we think about RiskMAPs and improving safety and quality in the medication arena. So it'll be a little tangent, but we'll come back and finish with the clinician perspective. And we'll leave, if everything goes according to plan, a lot of time for

audience discussion with the panel. And we're going to run things a little differently, but I'll tell you that when we get to it.

Our four speakers today are an incredibly -- well, I'm sure the whole room is filled with incredibly knowledgeable and accomplished people, but these four really stood out to me. Carole Flamm is currently the executive medical director for the Blue Cross, Blue Shield Association's Office of Clinical Affairs. She was previously the associate director of Bayer Technology Evaluation Center. She's an accomplished physician herself, as well as a fellowship training in epidemiology and health services research.

Our second speaker is Dick Wagner from Kaiser Permanente, where he's been for the last 25 years in many different capacities helping the Kaiser system understand pharmacy and pharmacy benefits. He's been a formulary manager. He's worked on their Drug Information program, physician education; outcomes research and pharmacy

benefit management. He's also a member of the California Society of Health System Pharmacists Board of Directors and has served as an officer with them.

Peter Glassman comes to us from the Veterans Administration. He's currently a staff physician at the VA at the Greater Los Angeles Healthcare System. He's a professor of Medicine and also on faculty at Rand. He's the co-director of the VA Center for Medication Safety at Heinz in I believe Iowa. He has a medical degree and his Master's of Science both from -- in Economics from the University of London and did his residency training in Connecticut as well as a fellowship in ambulatory care and health services research in California.

And our clean-up hitter is Dr. Wilson Pace. He's most importantly like me, a practicing family physician, professor of Family Medicine and the endowed chair of practice-based research at the University of Colorado. Bringing him to this meeting, he brings with him the perspective of working on the Institute of

Medicines Committee that produced the report, "Preventing Medication Errors." He's an accomplished researcher as well and highly funded.

So what you saw from the schedule, my ground rules, each of these folks is going to get about 15 minutes to lay out their story for you. And at the end of those, I'm going to -- we're going to try to leave one to two minutes for just clarifying questions, not the big issues, but if they used an acronym you didn't understand, or you want a little bit more data on one of their slides, we're just going to take one or two audience questions and then move on.

I'm their taskmaster and I rule. Going to really try to hold us to this schedule. And at the end, we're going to have the audience and panels. So I'll have all four panels come up in front of the room. And just to warn you, what we'll do is take questions from the audience all at once, question, question, question, question, question. And then I'll type those up, and then

we're going to turn it over to the panelists to work those out as a group and respond to those collectively, take turns and who wants to respond to what. But that way, even if we don't get to all the questions, we'll have the -- in our transcript a list of what are the issues that were concerned. And as that dialogue goes, we may turn it back to the audience for more questions or your perspectives as well. So with that plan, let's see if we can do it. Carole.

DR. FLAMM: Thanks, David. What I'm going to do in about the first 10 minutes or so is really speak from a fairly high level perspective bringing the view from one commercial payer organization, the Blue Cross, Blue Shield plans, in terms of how we look at medication safety in our role in helping to improve that.

Just to give you a little bit of a perspective, the Blue Cross, Blue Shield plans collectively provide health care insurance to close to 100 million members. So it's about one in three Americans. And when we have that

kind of population, I think we very much hold dear the principles of public health in trying to do the right thing for patients. So I think you'll hear that woven throughout some of the messages that I will share today.

We have a very active group of clinical pharmacists throughout our plans that meet regularly and meet face to face quarterly and discuss collective, clinical issues around pharmacy care. And they've recently endorsed a set of principles around how they address medication, safety and pharmacy benefits in general. And there's a strong commitment to evidence based benefits design practice in terms of pharmaceutical care. They want to provide choices. And understanding the evidence based on clinical evidence and expert consensus using independent P&T pharmacy and therapeutic committees as a critical piece in that they believe, of course, that it's the physicians' primary role to administer and take on the ethical obligation to provide accountability for appropriate individual therapy and make

those individual risk-benefit judgments.

We try to integrate together as much as possible pharmacy benefits and medical data and management. Sometimes that's a challenging thing in and of itself, but that's really the goal and the principle. And do see our role as helping to provide education to all of our stakeholders, including patients, physicians, the pharmacies and other caregivers that we work with to help promote appropriate use and compliance adherence. So we have natural relationships with patients or members, as well as the providers that we contract with, and the pharmacies that we interact with.

Some of the major groups of interventions or administrative programs that a health plan will put in place, most of them occur at the point of sale. And a vast majority of our plans responding to a survey do have point of sale type efforts to improve medication safety. What are those types of things? They are edits to look at dosage that's being administered, maximum units, edits for

looking at the gender age or duplication of prescriptions, monitoring for other contra-indicated drugs and combinations, and then there is components of drug utilization review programs.

As I mentioned earlier, there's a strong commitment to evidence based medicine and the deliberations of the pharmacy, and therapeutic committees formed the basis for looking at the clinical evidence for a variety of indications. Certainly FDA labeled indications come with evidence. But when you're looking at off label uses, these groups will look at the available evidence to ensure that there's adequate evidence of clinical effectiveness. Either in the literature looking at compendia -- you're all familiar with those processes. And they'll make various decisions relating to how to place new medications and various design tier programs, and co-payments are sort of part of the managed care side of things.

So these policies contain appropriate use

criteria, looking at indications, concomitant and/or failed therapies that may be required prior to using the medication question, so-called step therapy. There can be dosing guidelines, re-evaluation parameters for continued use, and then a variety of prior authorization type programs.

What do we do in terms of communicating with physicians? Well, we'll take on trying to communicate when there are new black box warnings or recalls. We will monitor pharmacy claims data for adherence and communicate to physicians on compliance for refills.

There's an interesting sort of trend that is becoming more apparent when you look at electronic prescribing that you can actually capture when a prescription was written, how often the patient actually goes in and fills the prescription. And it's unfortunately very, very low, much lower than people would expect. So there's a lot of opportunity for closing that gap as we understand more about the information.

So we'll monitor claims to ensure compliance with required tests when that's part of what we're talking about today. And then plans -- we'll notify physicians when their drug utilization review issues duplicate therapy, like I mentioned, unusually high doses, other contra-indications that pop up.

We will also communicate to members either through websites, newsletters, various disease management programs. These can be viewed as annoyances, or they can be viewed as other helpful ways to expand opportunities to communicate. And we'll inform affected members when there are drug recalls and new black box warnings.

So how do our plans work with RiskMAPs? We did try to canvas some of our pharmacists and get their direct input. The majority of plans did express a strong interest in obtaining information about current and new RiskMAPs so they can incorporate this information in their inner management prescription benefit programs. A number of our plans already do this very actively.

They did express that there's a need to have more centralized and available information on RiskMAPs and very much support the idea of a central repository or a website with RiskMAPs being easily available and accessible to the public. So when RiskMAPs are known, our plans may use them as a starting point for benefits management. And in some cases, the RiskMAP itself is adopted as sort of the basis sufficient to ensure safety of drug use.

Some plans may actually go a little bit beyond that and be in a position to help put in place use management programs that may not be within the purview of what FDA does within its regulatory authority. And so if a drug is risky and requires a RiskMAP, some plans will require a trial of a less risky drug, done in conjunction with the P&T type committees, and the same therapeutic class before approving payment of a RiskMAP drug, basically trying to help manage the public health and safety risks.

Plans can use elements of RiskMAPs in on-line edits at the point of sale as I mentioned. One example where the RiskMAP was certainly put into place through a collaboration with a vendor program, Tysabri, the vendor relationship they will actually take on the certification of providers and help to address that piece. The drug is not used as a first-line therapy in this example due to the safety concerns.

And when the drug is approved, the dose and interval guidelines may be imposed by the plan. Some of your basic stuff, but sometimes it's complicated to link together the medical side and the pharmacy side because different medications will come through under different billing systems. And so that's one of the challenges to put in place with these kinds of programs to make them work real time.

Wouldn't it be nice if we had electronic prescribing? I think there's a belief that automated E-prescribing and integrating of lab results at the point

and time of decision will reduce the reporting burden. Getting all of that timed right and in the right place is going to be a challenge. But the opportunity to link E-prescribing with patient records, and issue automatic alerts for contra-indicated drugs, drug, drug interactions of various quantity and dose limits is really the goal and the opportunity to make it more systematically possible to do the right thing in an efficient manner. There will be enhanced opportunities as that improves to support clinical decisions.

And obviously as we have more and more data available, the opportunity to look at patient specific adherence reporting is growing. Refills can be blocked when you have an electronic environment when that's not appropriate. And many of our Blue Cross, Blue Shield plans are committed to and have been supporting efforts to increase E-prescribing. That's still a work in progress.

One of the challenges of the current system -- well, we need more objective consumer education on disease

states that are risks and benefits of drugs. I think that was alluded to in the earlier panel from the consumer perspective. And I missed some of the presentations, but direct consumer advertising doesn't adequately address the effectiveness risk and alternative therapies. And there's really a need to have more of that available. More safety information is needed by clinicians, patients, and payers post-approval. So we're very supportive of this effort. We also need comparative effectiveness information. I think to make that proper balance of benefits and risks, we need to understand how the various alternatives compare to each other.

And then there is a need for a better care coordination across all of the various sources of care that a patient has and the various prescriptions that they're getting from different directions. The need for a medical home, I think other speakers may address this, is something that we're seeing as important from a payer perspective. And how do we get our various systems of

care delivery to communicate better with each other as a goal.

What are the rules for a health plan in this? Well, we can use RiskMAPs, and I think many plans are doing that. I think there's an interest in doing that more. Expanding the reach of educational and reminder programs through our own communication channels is an opportunity to help the message be heard from multiple perspectives and the same message. We want to align with prescribing and dispensing restriction programs as sort of a -- to avoid duplication and confusion, everybody kind of inventing their own RiskMAP would be a very difficult thing to adhere to.

There are opportunities for a national pharmacovigilance system that can be built on collaborating around some of the very large databases that we have available. And I think there's a lot of exciting opportunities with that. That's another whole set of topics that I know is being discussed in other forums.

But it's something that ultimately could fit in here. And I think there's an interest on the part of our plans to help evaluate the compliance with RiskMAP programs and the effectiveness of different RiskMAP program elements along the way. And that's all that I have if you want to --

DR. MEYERS: Are there any clarifying questions? Why don't you say -- I'll repeat it. Okay. Who are --

MR. TUCKER: Ed Tucker from (Indiscernible). One of your slides said that you were less (inaudible) with a product which has a RiskMAP. On your (inaudible) use that product (inaudible).

DR. MEYERS: So that was Ed Bayer from -- Tucker from Bayer Pharmaceuticals. And the question for the transcription was asking for clarification about Blue Cross, Blue Shield's ability or decision-making process that if a given pharmaceutical had a RiskMAP associated with it, is there tendency to go to a less risky in the same class medication.

DR. FLAMM: Thank you for asking that clarifying

question. I don't think it's fair to say that that's a blanket statement. I would say that when in the judgment of the clinicians and the advisory groups that work within plans think that it's a most appropriate thing to try step therapy, there may be specific circumstances when that may be the case. But I don't think it would be correct to say that it's a blanket statement at all. So thank you for asking that clarifying point.

MR. TUCKER: For those of us not in the business, what's an edit?

DR. FLAMM: An edit is sort of a stop or to ask questions or to sort of this needs to be in place for something to proceed through.

MR. TUCKER: Okay, it's not a mandatory check. It's just flat.

DR. FLAMM: I think so, and you could probably administer it in different ways, depending on how restrictive you want it to be. There are sometimes where it's just a reminder as well. Thank you.

MR. WAGNER: Okay. I'm from Kaiser Permanente California. My name is Dick Wagner. I'm a pharmacist. And although I technically work for the health plan, as you know Kaiser is really this large integrated delivery system. So most of my day I spend working with the physicians. And we try to really think through how we could make it easy for physicians to do the right thing. I'm going to give you two examples today of that. And it's really -- it's how we do business every day. I think at Kaiser Permanente -- when I come into work, I really do think this is how we need to work every day in terms of improving safety, quality and ultimately cost effectiveness too.

So what is clinical decision support? You're going to probably see this more than once today. It's certainly a systematic approach to make it easier to do the right thing. At the same time, we also want to make in same ways harder to do the wrong thing. So the focus is make it easier to do the right thing. I'm going to

give you examples of that, two examples today. But also we do -- keep in mind that you could also make it harder to do the wrong thing. That's also another important factor.

I want to go back on some work that we had done previously, and it's been reported in the literature in a couple of different fashions on Cox-2 drugs, and the risk of GI-bleed in our population, and what we did over the last several years to really try to minimize the impact of NSAIDs, and also the appropriate use of Cox-2's when they were more readily available. So that the patients who really needed a Cox-2 drug got a Cox-2 drug when it was appropriate. It was used based on safety, efficacy.

And at the same time as the Cox-2 drugs have dwindled over the time in terms of the ones that are available on the market place, we've taken another strategy in terms of NSAIDs plus a PPI to avoid the GI risk in our patients, GI bleed risk in our patients. I want to walk you through how we have developed that.

And these are really questions that our primary care physicians were asking. We basically like to work with our clinical experts, in this case a rheumatologist, who have a lot of experience using NSAID type of drugs in the prescribing for patients with rheumatoid disease or other diseases that they treat. So our experts in this area would be the rheumatologist within Kaiser Permanente.

So how does a prescribing physician decide when it's most appropriate and again this is a couple of years old. But the question's still relevant when to use a Cox-2 NSAID type of drug, and who are the high risk patients for NSAID induced GI bleeding that may benefit from a Cox-2 drug. And over the last year, couple of years, we've migrated that thinking into an NSAID plus a PPI, and I'll show you an example of that. So these are questions that we try to answer.

The population issues that have been discussed so far are very important to us. But also when a physician is taking care of a patient, they really need

guidance for that particular patient. But what we've really tried to do over the past few years is provide patient specific guidance on risk so that the prescribing physician can incorporate that analysis into their thinking, into their prescribing, and into their discussion with the patient about what's the right drug for you, not just the population. Want to do what's right for the population. But what is really the right drug for this patient and my medical office today, and can I provide that physician with information that could help them make the right decision today.

Data that we had worked with, we had -- Stanford had developed a way of stratifying patients in terms of risk for GI bleed. But if we're going to take care of -- and I'm specifically talking about the six and a half million patients in Kaiser that we take care of in California -- that we needed to really automate that system because the physicians are seeing patients. We have electronic systems that can combine hospital data,

laboratory data, pharmacy data, demographic data, and how do we put that together. And so one of the things that we worked on was could we automate in essence what the Aramis database was providing to physicians through the work that Girga Pulsing (phonetic) and his colleagues at Stanford had done. And I'm going to give you a reference here.

So if you look at the -- kind of the pink line or the light line, you'll see that was the estimated one year risk. When we went back and looked at our population, the blue line really reflects our own internal data that really superimposes very nicely over that curve line there. So we had a high degree of confidence with our data, this administrative data set, that was updated every 24 hours. So physicians always had current data when the patient came into the medical office. We could provide the physician for that patient they're seeing today with their risk assessment for a GI bleed.

These are rates that we had determined internally in terms of correlation between GI event rate a

bleed per a hundred patient years of inset exposure. In essence, what we really saw was -- the highest risk was what we called risk level four. These are patients that scored very high on the risk assessment, very consistent with the Aramis data, very consistent -- or internal data was very consistent. The patients at risk level one, two or three were really relatively low risk for a GI bleed and could do well absent -- no, again a physician may know something we don't know, but our administrative data would suggest that they would not be candidates for a Cox-2 at the time or an NSAID plus a PPI right now.

This is from your humble presenter, this is actually my medical record information. I pulled it out a couple of days ago, and so that too. And so my risk level is a level two. I actually have 12 points up on the system, translates into a risk level of two. I'm at relative low risk for a GI bleed. A physician seeing me in the medical office would have access to this record, or this information. And they could use this information

plus other information that's presented to say yes, you're a good candidate for X, Y, Z NSAID. And here's some information, you know, that would be used to guide that thinking.

So over there, the patient's NSAID history on the right. Luckily I just got four kids that need care at Kaiser. I don't get too much care myself, but you can see on the right is my drug history, my acetaminophen history. On the left -- left as I'm looking at it, so it's probably -- left is drug, right is other things around hospitalization. And you can go down here and see how this is actually quantified in terms for the physician.

So in addition to giving you a score for the busy physician, score of two, we give you all of the information we used to calculate that score. Again you might know something about that patient that may be new to Kaiser. There may be things that haven't been captured. Hospitalization records get updated about every 30 days. The records for all the other aspects, pharmacy, lab and

other things, are updated every 24 hours.

And what we have learned again over time is that if you provide physicians with real time, updated information that's accurate and you put it in front of them and it makes sense and it's endorsed by clinical experts, like the rheumatologists, lo and behold, they basically follow true with using the risk assessment.

This was a previous example that was a piece of paper. Some of the physicians actually put little things in their pockets and their white coats and walk around and pull things out. So one of the things that we've also learned to do with physicians is you don't just take one approach. Some people work really well off the electronic chart, the Internet. Some want a little piece of paper they can put in their coat and they can actually refer to. Either way, whatever works, we're going to give people all of the alternatives, and this was an example. It's a little bit hard to see here, but it'll be on the slides. It goes through the same thing. So a physician that did

not have access to the electronic system, could actually score you if they had access to the other information that's on this little piece of paper.

So what's the Kaiser Cox-2 story for us? This was back in the 1999 to 2001 time frame. Like most of folks, Cox-2's were starting to grow very rapidly. We think related a lot to direct to consumer advertising. We were looking at this thinking it did not make sense, either from a safety perspective, because if you go back and look at the Vigor trial, it did actually say that Vioxx did have additional risk, and it didn't look like people were taking that additional risk into account in our own plan. When a rheumatologist looked at it, and you can do this by pulling charts or through electronic systems, we decided from a safety quality perspective we had to make an intervention.

Intervention was made in early 2001, and intervention was designed to do what we typically in the past had not done very well. And that is on a patient

specific basis, make sure that the doctor had what he or she needed to assess the risk of that patient properly in the medical office.

So yes, education's important. All of the things you could do to remind physicians are important, but they're not enough by themselves. You really have to fine tune your systems down to that individual patient and the risk assessment. Let the prescribing physician make the last decision. They're responsible for the clinical care of the patient. But it's very much focused on the risk assessment for that patient.

And over time, this thing has really dropped off quite suddenly. The Cox-2 story in this country was about 45 percent or 50 percent of the NSAIDs prescribed in this country at one time were a Cox-2 drug. But then Kaiser Permanente had stayed at about 4 or 5 percent. That was actually justified. As we looked at our own internal data, said, you know what? It's about 4 or 5 percent. It's about the right numbers. It doesn't make sense that

this is a 45 or 50 percent thing. So we are actually confident that we're doing the right thing. And then lastly we're a well positioned when the box recall came about. And Cox-2 use now is about less than 1 percent in our program. And again, we provide that back with the physician to make the right risk assessment.

It's controversial. Can you say that we did something here? Avoided 400 deaths in southern California. I mean from an epidemiologic standpoint, some would say you could make that decision. We have shared this information with large purchasers like Calpers (phonetic) who will tell you of all the plans they work with in California, California did the right -- or Kaiser California did the right thing. It was very difficult when you go back and look at Calpers with a million members and they really do think that their member -- those are their members, their employees and retirees. There's about 400,000 of those people. So Calpers was very interested in this story. And it's very important

that purchasers actually are interested in this story because they are paying the bill really. So that's one story.

The other one is -- and I'll stop there and take a breath. I'm going to move on to one other one. I'm trying to give you two real-life examples in Kaiser Permanente. There are many more but these are two that we've actually reported, we've written about in the literature, so there are things that could be reviewed, things that can be shared, and hopefully others could adopt similar strategies and programs.

But I want to talk about one program that we have reported on for about -- several months ago in the American Academy of Dermatology, and that's about our KP MedSmart program which was modeled after a similar program between Roche and the FDA, the Smart program that was in place. And when that program first came up, the principles of the program made sense to us. We wanted to predict women -- ensure that women would not become

pregnant on Accutane, or were not pregnant and then started on Accutane. But we had concerns about the little yellow sticker, so it was a procedural thing. So one of the things that we were trying to really push is that we can agree on goals, agree on principles, agree on standards. But we really do want some flexibility around procedures, especially if you're in an integrated healthcare delivery system and has an organized way of delivering care. Flexibility around the procedures can actually make the thing more successful we believe.

So what we really try to do with KP MedSmart is link the dispensing of Accutane or isotretinoin to a required negative pregnancy test using our integrated systems that are in place. So if you could imagine when I go in and take my four kids and Karen to Kaiser Permanente, the medical office, there's a pharmacy, there's a laboratory, there's medical offices, probably radiology, and several other services. I would say typically pharmacy and laboratory are on the same floor,

typically first floor. And getting laboratory data is very easy because the systems are integrated.

And if a patient does not have a negative pregnancy test or pregnancy test on record, you can actually send the patient over to the laboratory and get that pregnancy test done, or she can get that done, and it'll be back within 30 minutes or an hour typically. So that's the environment that we're in. Some of these things may not work if that environment doesn't exist, and I would readily acknowledge that.

The other thing we did with KP MedSmart was to create a registry of female patients. We wanted to track and trim this over time and provide at our medical center levels where quality is assessed and reviewed periodically information back so they could actually say, yes, we're doing the right thing for each of these patients. They're getting Accutane or isotretinoin based on the standards of the dermatologist has set for clinical appropriate drug use of Accutane. But also we want to make sure the

monitoring and avoidance of pregnancy while they're on this drug is something that we can assure.

What we really had to do is a couple of things. One is we did approved policies and procedures through our P&T committees. And that was designed to ensure medical group buy-in and dermatology buy-in in terms of clinical champions. And just like with the rheumatologist and the NSAIDs, we had to go back to the dermatologist and Accutane. And they're by far the most -- 90 plus percent in terms of prescribing this drug. We want to make it easy for the patients, but also we wanted the patients to know why we were doing this. So if it was easy to do, and if you planned up front it would be no delays, but if you didn't do it, we were going to send you back, and we were not going to dispense that drug until we had a negative pregnancy test on file.

I will tell you most of the patients get it if you sit down and explain to them that you're concerned about their safety. And it's designed to ensure that

everything is working as closely hand-in-glove as possible. Very few patients actually complained, and most of them got it, and it worked very well I think from a patient perspective.

Well, we reported back in the Journal of American Family Dermatologists. Ninety-eight and a half percent of the patients had a documented negative pregnancy test prior to dispensing. So that was something that we could from a quality standpoint assure. Actually no patients with a positive pregnancy test at the time of dispensing actually received a drug. So very high rates of compliance internally over several thousand patients.

This all came about because before isotretinoin went to became a Sub-Part H regulated drug, it was regulated through product labeling. That product labeling, at least from our legal folks perspective, and I think the FDA gave us great flexibility in terms of, you know, we didn't implement the SMART program. We implemented something we thought was as good or better.

Although that should be allowed to stay or not, that's exactly how we approached it. However, it's become a Sub-Part H drug in terms of regulation. We've had to transition to the iPLEDGE program. And that's just -- you know, you've got to be compliant with the law too. We've got these corporate compliance folks in our organization.

So what we actually found out, though, we did all this work. It was actually very enthusiastic. Quality was being tracked, but then we said we got to sit down and take a look. Let's look back and did we make a difference in the lives of our patients. In other words, did pregnancy rates, while patients were on this drug, actually decline? And we did a lot of work, identify the cohort and do the research. And what we actually found out within our own program, this very intensive monitoring and assurance of negative pregnancy status before you got the medication resulted in no change in terms of our actual performance. And, you know, at first we thought that was just horrible. Now maybe at this we're already -

- maybe on the low side in terms comparison. So it was already low, and it's hard to get better than low because these are very rare events.

But what we actually identified as we reviewed the charts of the patients who did become pregnant separate than the data systems was the failure of the patients to adhere to all the risk management procedures related to becoming pregnant and Accutane was the real issue. It turned out to be patients agreed to behave a certain way, but then reality -- and then actually probably in reality most did. But the ones who became pregnant while on the medication did not actually carry through for whatever reason. And it certainly turned out to be from our perspective reviewing the charts, it looked to be more behavioral in terms of their own -- they'll say one thing and actually behave differently. And why that happens is -- research will have to be done to help us on that question too.

I'll just finish up here with an integrated

delivery system viewpoint. If we could establish clinical standards with flexibility and procedures in the systems to meet -- and we'd want to meet or exceed the standards. In other words, let us define the procedures used in our systems and our technology, set very high standards. We should meet or exceed those high standards. The reporting of that should at some point be back in peer review literature so it can actually contribute to how everybody else's practicing, and we need to do that rigorously.

Data collection's absolutely necessary. One of the concerns we have with the iPLEDGE program -- I don't know how data collections happening. What we're probably going to do internally is take a look at -- after we've implemented iPLEDGE within Kaiser Permanente by isotretinoin -- how are we doing to impact the iPLEDGE on our system.

Reporting to providers as part of quality management processes, physicians need to know where they stand in terms of actual performance. They need to know

where they stand relative to their peers, and they need to know if there are outliers, a patient of their's became pregnant while on this drug, has that been reviewed from a quality review process by the medical group.

I know all this may be -- it may take regulatory changes or statutory changes to put some of these things in place, but these are some of the ideas that we've had. I'm going to stop there and just leave the references. They'll be in the slides. These are two things again that we've published at Kaiser Permanente to hopefully support the conversation we've had today. I have a series of slides after this that I'm not going to go through. Some of it's been discussed.

One of the things that we have learned in terms of improving safety and quality prescribing is to learn from the folks that do disease management or care management. But there are processes that people have invented already that we can adopt in terms of safety and quality management. So there's a series of slides after

this that you can use as an appendix that referenced how other people have tried to influence positive change in the healthcare system. Typically the population management, disease management people are very well acquainted with these slides. So I'll stop there and take questions. And thanks for your attention.

DR. MEYERS: I'd just like to ask folks to go to the mikes and introduce themselves if you have any clarifying questions of Dr. Wagner.

(Pause.)

DR. MEYERS: Okay. Perfect.

MR. GLASSMAN: Hi, everybody. Thank you for inviting me. When somebody mentioned workshop, I always have the image, or sometimes have the image of a small table of people with their sleeves rolled up. I didn't realize there'd be so many people working or shopping, depending on whether you have Internet access right now.

So this slide's just to point out that we're a large integrated system that goes from over there to over

there and a few other places. We're big. This is where I work. It's in between there and there. Choose.

So the VA maintains a list of drugs with closed ordering on its Internet website, and this is just to give some background. It gives information on the drug, the company where the drug is -- the manufacturer, I should say, the requirement, whether it's an FDA or manufacturer. Whether the drug's on our formulary, the process of the PBM website link, and a company in the pharmaceutical website where you can get more information on the drug.

Here's some of the drugs that are on the list. I've starred clozaril because I'm going to talk about that in a little while. Some of these drugs you've already heard of today, so I won't go over them all for the time. So here's an example, thalidomide, the company is Celgene. It has special handling, closed ordering distribution system. That's an FDA required -- FDA requirement in safety. It's not on the VA national formulary, and it's run by the STEPS program where you have registration of

the physicians and the pharmacists.

Now I was asked to talk about the VA clozapine program. I, myself, don't really get involved too much in this. I'm mostly on the P&T levels at various levels in the VA, but I think it's an important illustrative example of what can happen. The VA received authorized vendor status. It developed an outpatient program where it tracks blood counts weekly, bi-weekly, monthly, depending on the requirement at the time. And it prevents a prescription from being dispensed without appropriate white cell count. And it's the difference between a pro-active and retrospective assessment. There is some limitations to the program.

This just happens to be an illustration of the protocol done in 1999. It's being updated, so I'm told. The important thing is not the actual protocol itself or the words in the protocol, but rather that there is protocol and procedures for doing this that the VA has established as part of its clozapine program. This is

just an illustration how clozapine has increased over time in the VA. And as you can see, it's gone from -- it's increased steadily, though not dramatically over the last, what, five, 10 years. Still keeps going up.

And in terms of its processes, the program just stops the dispensing if the requisite blood cell counts are not there. It aggregates data. I'd like to say it's completely electronic, but I'm told it isn't. It's by a combination of electronic as well as paper based or fax. And it generally meets about 95 percent compliance with FDA requirements for a single week. And I was given an example from January. So there is some fluctuating numbers there, but by and large, it's a very compliant program, which is obviously very rewarding to see.

We've already talked about evidence based prescribing. And again the clozapine program is an example of what an integrated healthcare system can do when it has patients, physicians and data in alignment.

Obviously we as a healthcare system have to deal

with new drugs and old drugs too for that matter. And the monographs for the new molecular entities for this example, we obviously are wedded to the idea of evidence base medicine. So we develop evidence base monographs, and we develop evidence based criteria. And I think the key thing is to understand that in an integrated healthcare system, we have people on site that can help implement these programs. And by and large, these drugs that are high risk are going to be implemented locally under fairly strict requirements or strict supervision.

And here just an example is what a typical monograph would look like. We obviously -- this is just a front page, and we generally have an executive summary on it that lists the efficacy in safety. Again not important exactly what this says about this particular drug. Just suffice it to say that we have programs in place and people that are doing this that work on evidence based monographs for the high risk drugs.

You often see -- in these monographs, you may

see criteria for the use of the drug within the document, or in some cases, you'll see it outside the document. In other words, it'll be a stand-alone document and criteria. And the point of all this is that all these are on our Internet website should someone want to go see them or need to provide them to a provider. They're there.

And typically what happens is a provider at the health center will want a particular drug. Obviously these are the high risk drugs. They'll be reviewed by a local P&T or a delegated person. And that delegated person may be a specialist, or it may be a person that's associated with the P&T. There's a variety of different ways to go about this. But the idea is to try to assure that it meets criteria or is granted an exemption for whatever reason. And then the prescriber would continue per local regulations or for federal as well as local regulations, now obviously for local procedures. And we may, for example, say, well, you're welcome to try this drug, if it were an exemption, for example, for three

months. And then at that point, we need a re-evaluation. We need to know what happened. So local centers can do that if they want to.

So I want to go on to something that is a little bit near and dear to my own heart. And that's what I call Smart prescribing. And the concept of E-prescribing, if you will, is using available technology and resources to improve and guide clinicians, improve prescribing and guide clinicians. And the goal is obviously to increase -- it's not just safety. Its efficacy, safety, monitoring, and of course, outcomes because that's what we're really all about. There's no point in giving a drug if you don't have a better outcome in the long run, or at least try to have a better outcome in the long run. And I wondered if some of these things that we've done can have applicability for RiskMAPs, or at least associated practices.

So this is based on a slide presentation I did a few years ago in 2004. I updated some of them, and these

are some of the people I worked with. You'll see some names through this, ways of saying thanks and acknowledging their work.

So our technology, CPRS, is a computerized patient record system. It's our electronic health record. This is circa 2004, but essentially the same thing. Obviously our objective is to guide appropriate safe and cost effective drug use. Options for Smart prescribing are somewhat limited by the technology. In other words, all technology is going to have limits, but we can use that technology. We can co-opt it, if you will, to try to create a better prescribing system.

And these are some of the options. I merely point these out. You'll see them in a minute. There's one that I'm not going to show you which is medication utilization templates which was developed by a friend and colleague, Dr. DeLill (phonetic) at Baltimore -- and his colleagues at Baltimore VA.

So the consult menu. We talked about this a

little earlier. This is what we use a lot for prior authorization. And I'm just going to give you a quick example. There are templates that we can build. They are often point and click because I have to adhere by the same policies I develop. So for me, I want to be fast in clinic. So I want it easy, I want it fast. And if I have to argue with somebody, it's going to be me. So that's going to be a problem. And it's very embarrassing when I've been turned down for my own drug request. I want to point that out. It has happened. Do you really want to do this? No, thank you.

All right. So you have to be careful because it does interrupt the provider. This is a more complex situation. You can see that this is an example of our cilostazol, or platol template, where we ask people to click and -- or point and click on relevant issues, clinical issues and otherwise, that we want them to deal with. Again it's just illustrated, and it's not that important exactly what it says. But the point is we can

create these and create a more, if you will, hopefully a more effective prescribing environment. Again, though, have to be careful with it. It takes time. Precisely what I don't have usually.

So this is a clinical reminder technology, and this is readily available through our electronic health record. And we can make it trigger on a whole variety of things. So I could check, for example, if a patient on a-typical anti-psychotic has had Lipid profile within six months. Now it comes up in a separate part of the record, and you have to go to it. You have to know to go to this. And that's why I said it doesn't provide real time advice. It doesn't just pop up right in front of you and say hold it, think about this, but it is there.

And here's a typical example. We designed this a few years ago to be part of a pain medication use agreement for people on chronic opioid use. And it directs the provider to do, as it were, the right thing, both for him or herself and the patient and the healthcare

system. It gives a series of options you can click on. You can fill it out, or you can go look at the pain -- if you clicked on that, you'd see our pain contract policy.

Now this is -- again these are things you can play with in the record. A lot of this is already established, like the basic prescribing template. But you can use this to help -- so for example, here's the basic template for a drug benazepril. We can use a default dose, a schedule, a root. You can do a lot of these things, and of course, you can leave them open, and the prescriber can fill them out. And you can see down below it gives the sig.

And here's some of the things I can do, or we can do. I don't do them. I don't know how to do this. I sit down with our Ad Pac and she does it. So we can put up on top -- we can put a display restrictions guideline which I'll show you in a second. Or we can put a pop-up box below, which pops up if you push on a dose, you click on a dose. So here, for example, is if you click on

display restrictions guidelines, it tells you how to dose the drug. Again it's just another way to try to add -- I won't say it's fail-safe because clearly you can get around it, but additional system to help prescribers do the right thing.

Now there are ways to set up quick orders. Quick order is just a rapid template that you can use to try to get people to prescribe quickly. Some providers use them. I do, myself. Sometimes other providers will use the main electronic menu. But again, it's not to be a be-all and end-all. There are ways you can close off the main menu and only use quick orders. We do that for some drugs. But by and large, it's just another way to help providers.

It's very quick, very easy, but here's what you can do. Here's a quick order screen where a number of quick orders are already set up, and click on benazepril. And in this case, I've stopped the prescribing process. Again, it's not me. Stop personalizing this. We stop the

prescribing process by bringing up this template. Now the provider can go right through it, but at least it provides a mechanism for getting the information very quickly during the prescribing process that you want to get to the providers. And once you click on okay, there you are. You're back at your template. And again, you have the same blue line above, and you have the pop-up when you press. So there are overlapping mechanisms in some cases that you can use to try to get that message across. Can they ignore it? Of course.

All right. So here's what you can do with quick orders, which is what I just showed you. You can build decision trees very quick. Here's an old decision tree. We don't use urbasartin (phonetic) generally any more, but at that time, an urbasartin was available to people that had an adverse drug event to an ACE inhibitor. Well, if I wanted them to put in that adverse drug reaction, I could create a decision tree and said if it's yes, they have already documented the AD, they go on to prescribe. And

if it's no, it would take them to the menu to put in an ADE. So now I have a mechanism to capture ADE's as well as get the information I need.

And here's a more complex decision tree, again illustrative, but I can guide providers to where I would like them to be, or we can guide providers to where we would like them to be very easily and very quickly. And not only do they get to where they need to be, but the system benefits as well, and obviously we hope the patient does, being that's the end-product goal.

Decision trees can be much more complex. This was set up by colleagues of mine at the VA where we -- where you could choose the condition that you wanted to treat. And I really like this because here you have a template on bronchitis. It gives some very simple guidance, and it lists our preferred medications.

Now the beauty of this is let's say next week we decide we want a different medication on this list. It's as simple as going to our Ad Pac and saying, okay, would

you replace, I don't know, doxycycline with whatever drug it is that you want, and it's a very quick move. We can then -- the providers will just be taken to the proper place and they will go to the same place, but it will be a different drug. We will control that underlying logic. They will benefit by having very quick access to the drugs that they would want to get. It kind of goes back to Dick Wagner's idea of we want to make it easy to do the right thing. And here is an example of the bronchitis screen where if -- go all the way down. You can see the moxifloxacin. So it lists the other medications that can be used if needed. And when you click on it, it opens up.

This is a checklist. This is a mechanism that can be used to help guide prescribing in a way where you want providers to have a certain amount of information when they prescribe. Again these are a little bit more difficult in terms of what providers need to do as you can see because you have to actually read it, and you have to check it off. Can providers just check and not read it?

Of course, they can. But the idea here is again to try to help guide people who may not prescribe these all the time. This is our primary care practitioner, amiodarone on the checklist. Why do we do this? Well, a lot of our patients on amiodarone go to their primary care practitioners, they don't want to go to, and they don't need to go to cardiologists for the most part, except for intermittent visits, so we make it easy. But we also want to make sure that the primary care providers are doing the right thing.

I don't know about anybody else who prescribes amiodarone, but I don't do it very often. So I can't keep it in my head exactly what I'm supposed to be doing. But the checklist gives me a hand. And again, we can also create the template once they get to it, or they can click on display restrictions and guidelines and that information would come.

And here are examples of vardenafil, quick order. Again it's a matter of safety as well as efficacy,

what the requirements are. So this can reinforce the ideas you can use checklists to reinforce the issues of drug safety. The newest one -- oh, yeah, here it is. Patient's been counseled on the potential for sudden vision loss. The beauty of this is let's say before the issue of sudden vision loss came out for vardenafil, we obviously didn't have that. But it takes all of about five, 10, 20 minutes to sit down with an Ad Pac, our applications coordinator, and add that in. Or if something else is subtracted later, we can always take it out. It's not a hard process. And once you have the electronic medical record in place, or E-prescribing in place, it becomes much easier. And that's it. It's one of the few times I've been completely clear on --

DR. TRONTELL: Wait. There is one question.

DR. RACOOSIN: I just had a quick clarifying. Judy Racoosin from FDA. How many people do you have working on putting these safety screens together? I mean is it all centralized at the Heinz site or how do you -- I

mean how big a group is it that you have putting in these safety screens?

MR. GLASSMAN: Those are all done locally. I should have clarified that. Those are all done at my own VA. And there is no centralized way. When we do create criteria, you can upload them into a checklist, and then it's up to the local P&T's to decide how they want to do that.

But all those were done pretty much by one Ad Pac. You're often sitting down with -- all one CAC, sitting down with one person. In the case of the antibiotic screen that was done by my colleague who's a pharmacist in ID -- her area of interest is ID -- and the other one, some of them were me. So we're sitting down with our Ad PAC's. So it doesn't take a lot because you can change an entire system as long as you have the ability to change all the screens.

DR. RACOOSIN: So then this is unique to your VA hospital?

MR. GLASSMAN: Yes.

DR. RACOOSIN: So then there would have to be people, like-minded people as yourself in the other VA's to do this? It's not automatically adopted across the --

MR. GLASSMAN: There's ways to share technologies, but that type of thing -- a lot of those things, for example, would need to be built locally, and also built to your own resources and who's going to provide, but it's all very straightforward. You do need though -- that's a good point -- you do need to have the people available locally that can do this sort of work. And some places of course are going to be resource constrained as opposed to other sites that will have more resources.

So that second part where the first part was really the VA more at large. Whereas the second part was what we've done locally to try to create a safer prescribing environment. But we're certainly not alone in the things that we've done.

DR. RACOOSIN: Thank you.

DR. MEYERS: Anybody else?

DR. PACE: Okay, well, I certainly feel like the small person up here compared to all these other people. We've had Kaiser and Blue Cross and the VA, and I'm here representing the four and five person and one-person doctor's office, okay. Little bit different issues of resources. It's pretty difficult, even if you have any MR to put in place in a single person or five-person office all the systems that Peter just described.

So some key points. There will be some overlap, but some key points of this talk is that talk about primary care as a critical access providers in this country, and that we do need to pay attention. So we heard about a whole lot of RiskMAP drugs. We talked about dermatologists with Accutane and other drugs here coming from mostly specialists from the big systems. And I'll show you what that means in a few seconds, about what that means as you take that to the rest of the country.

Talk a little bit about the clinical decision support. Hopefully a little bit differently than what Richard talked about, talking a little bit about hard stops versus soft stops, what it means, the effects those could have, and talking about RiskMAP programs as how they fit within that. Hopefully talk about avoid "steering by the wake." We do a lot of that in medicine, and we'll talk about what that means. And then -- we're really at the tip of the iceberg for whatever we're dealing with today.

So here is what happens if you take the family physicians out of the country. Everything in red has now become a health manpower shortage area. Everything in pink is a -- I mean actually, yeah, there's a shortage area. Everything in pink is with low ratios, and just the white areas are adequately covered. So can you find the white in there? There is a little. This does not take out the general pediatricians or the general internists. Once you do that, this map turns virtually red for the

entire country. Okay.

So really we are important. We do matter how we take care of these drugs. And a lot of them won't -- we don't deal with very often, but you have to think about those people in the middle of that country right where I am in here. You have to drive a very long way to get to anybody else.

What do we know about primary care? Just in case -- once again, this is a small person's perspective on where things are at, but primary outcomes do matter. There's just a wealth of literature that this country seems to have a very hard time understanding, okay? Countries with strong primary care systems have better health outcomes for less cost than countries that have weak primary care systems. Example, United States, okay?

States within the United States, states with higher ratios of primary care physicians and specialists have better health outcomes at less cost than states that have higher ratios of specialists. At the county level

within the United States, counties with higher ratios of primary care physicians or specialists have better health outcomes at less cost than counties that have more specialists.

At the individual level, individuals who access primary care have better -- you got the story, don't you? Okay? In fact, if you look at medical inequities, locations, counties that have higher primary care ratios have less inequity based on social economic status and race than the opposite. This is a pretty clear picture about what we need to be considering here.

Unfortunately in this country, primary care right now is on the edge. It's a system ready to collapse. Primary care income is falling. Many doctors in primary care now are earning less than $100,000 a year. That's still pretty high. I understand, but when you start to take into account that the average medical student comes out of medical school with close to $200,000 in debt or more, that just doesn't look like something

they're willing to try to take on. Limiting billing options are highly tied to time, very difficult to change. And so my amount of income is fixed, and my rates, the costs of doing business are going up, while procedural specialties are still continuing to gain. Cardiologists and nephrologists in this country are now earning about five times that on the average.

New graduates are choosing other fields. The workload is really unrealistic. The two studies that looked at what it would take to provide just preventive services and chronic disease care in a typical panel of primary care patients, get rid of all your acute care, get (indiscernible) line of surgery, anything else we do, by 17 plus hours a day. That doesn't -- and then you wonder why -- early on we heard that 50 percent of everything that we're supposed to do is done. Well, that kind of computes, doesn't if? If I even see patients for eight hours a day, I don't get to 50 percent.

So my perspective is that we need to pay

attention to primary care and start dealing with RiskMAP. We need to understand its effect on primary care. Anything that requires time, even a little bit of time, is a huge burden in most of the field if you're working off of what you see as opposed to a salary, okay? It's a huge burden in an already ready to collapse system.

Let's turn a little bit to clinical decision support. Clinical decision support, as you've already heard, is a synthesis of functions. It requires two levels of synthesis to get this done. First it requires clinical knowledge that is sufficient and logical and actionable. Sounds very much like what we heard about RiskMAPs this morning, right? You need actionable decisions. And then to be able to do it right, you must have the right data at the point of care and provide it. So it takes two different steps to get clinical decisions support correct. You've already heard that.

A couple of examples about how things go wrong. The current asthma guidelines -- there are new ones

posted, but they aren't accepted yet on HLVI's website -- the current asthma guidelines, the first thing you must do before you can start using those guidelines is you must determine the severity of asthma for the patient off all medications. Nobody's going to take their severe asthma patients off all medications. So the first step is impossible to actually complete. Then you wonder why these guidelines have never really been successful? Okay.

The medication is what we're more interested in here I believe. And if you look at the medication clinical, the support systems, we know -- I think most of you are aware that they're woefully inadequate. There are three major companies that provide medication information in this country. If you take in moderately complex patients, not the kind of people that we all see very often in our practice, but just the moderately complex patient, and you prescribe them a new drug and run them through these three separate systems, they only agree about 30 percent of the time on which interactions exists,

how important they are, which ones you should pay attention to. Basically it means that you really have a very hard time believing most of the stuff that comes up on my pop-up window, which I get how many times a day. Makes it very, very difficult.

One of things that the IOM committee recommended is that we need to take charge of this, and we actually asked AHRQ to try to take care of it. We know they need money to do that, but this is critical that we start getting this information correct.

A great example what I got just yesterday as I was ready to leave was a patient my pharmacy (indiscernible) person sent me one of them. A patient who had been on warfarin and levothyroxin for about four years now. And I got this major message that these two interact, and don't I know that I better make sure that I'm careful about these dosages. Well, these are two drugs we monitor regularly, okay? I've got a (indiscernible). I've already got the TSH. Four years

later, they have to send me a warning? Seems a little out of sync.

I'd like to point out that detail is critical. I think Richard covered some of this, but I want to make sure to pound this home, okay? If you get things even a little wrong in clinical decision support systems, take what we talked about for medications, clinicians will ignore them very quickly. Something as simple as Pap smears. That seems very simple, okay. Just remind somebody to come get their Pap smear. Turns out to be really complex and you better get into it. Some of them need three Pap smears in every six months. Some people need them at 12 months. Some people can do 24. Others 36. Others shouldn't have them at all, but they get them all the time, okay. Why even put that on our head? So for something as simple as that requires good decision, an update is rarely available very easily in the MR's.

A classic example was the fierce decision support for MI's that were put into emergency rooms. Put

them in emergency rooms. It lowered the number of people that were sent home with an MI dramatically. It increased the number of people who were admitted inappropriately. And it sent more patients home that didn't need to be admitted. So they had one fatal error. It missed what are called posterior MI on a regular basis 100 percent of the time. As soon as the study was over, every emergency room that had the software in place threw it out. Threw it out. They did better care when they had it. And it's not that hard to think, you know, I'll think posterior MI before I send this patient home, but no, they got rid of it. So you have to be very careful about the details.

I think we're moving to a different direction in decision support, and how this plays into RiskMAPs, we'll have to think about a little bit. We're moving out of the concept that we tell people what to do, and we're moving into a modelist shared decision-making. We now have so many things we can potentially do, and we're just on the tip of this iceberg. Wait till pharmacogenetics comes in

and everything else. We'll have so many potential things we could do to you that you're going to be wanting to think, well, what should I do. And that requires a much higher level of decision-making.

The best one I know of is the Archimedes model for diabetes. If you go out on the diabetes website, if you're not familiar with it, go out to Diabetes PHD. It is a wonderful program. Plus you find out after doing all of this other stuff you can do for diabetes, that if you can get people to control their blood pressure, put them on a baby aspirin, get them to exercise, that you get 80 percent of everything you can possibly do with every other drug you can throw at them, okay? They're not additive. You don't keep getting the same amount. We study everything isolation, but not additive when you start putting them together. I believe this is where we're headed in -- it'll be interesting to figure out how RiskMAPs start to take in things of this complex.

And the last thing about decision support, I

want to talk briefly about hard stop and passive approaches. So what you just heard with that screen that was available that Peter talked about, you could go to if you wanted to find out information about drugs or information, that's a passive approach, okay. So it's I as a physician have to do something. The computer's very passive.

The classic information support within EMR's is what we call soft stops. We showed you a whole bunch of those. I can blast through them if I want to. What do we know about them? We know that if you're a pharmacist or a physician, 95 to 96 percent of the time, you blast through them without reading them right now. That's what we know about them, okay? Pharmacists say they're only 5 percent of them, but when there are actually people out there watching, they blasted through a hundred percent, okay. So in fact most pharmacists will tell you to prescribe a drug X, I know it takes seven returns, okay. I just go seven, one, two, three, four, five, six, seven. Good.

Now I can try the drug, okay? The pharmacists who are in the room, is that right? They count them. They know what it's like, okay.

And a heart stops about what we're talking about here -- and I believe we should consider that a lot of what we're talking about for the RiskMAP programs, these are often hard stop programs. Hard stops says you can't do something, and you can't do what you want to do until you give us this information.

So what do we know about hard stops? Okay. First, they're not used very often. Where do you find them? Well, you find them in hospitals. You find them in operating rooms. Before you can operate, you got to do X, Y, Z. You find them in hospitals before you can dispense an antibiotic. You can't do this antibiotic until you get that consult, okay?

Selected studies. They tried to put in place in our hospital at one point in time that we couldn't get a CT angiogram for a pulmonary embolism until you had a

dimer. Ridiculous, okay? Finally (indiscernible). But these are people who need the study, the negative d-dimers. You see them in oncology, chemotherapy. You must have this set of data before we'll release that drug. I think that a lot of places have gone to hopefully a lot of these programs because this is an area where this has been shown to work pretty well. And of course, we see them with insurance companies all the time, okay? You cannot order this test until you call us, okay?

How are they accepted? I think mostly hard stops by physicians are considered to be a pain. But truthfully if they work and they provide better care, then most of us are fine with them. If there's reasonable ways to provide that information, then hard stops are not considered a problem at all. Operating room people are not fighting their hard stops, okay. Chemotherapy, I don't -- when I talk to my oncologist, they don't fight their hard stops. They see their hard stops as helping them make sure they don't have a (indiscernible) activity,

okay?

On the other hand, hard stops are not without problems. A well known experience of the pediatric ICU in Pennsylvania, they were going to be really careful about their drug use, so they were putting in a new computer physician ordered entry system. Their goal is to improve safety. They put a whole bunch of hard stops there. And they linked the hard stops to the dispensing, probably a Pixis system because that's what most hospitals have. You couldn't get that Pixis door open until you entered and went through the hard stop in the computer.

Then they step back and they look at what happened. And what happened? The death rate went up. They totally did not take into account the work fashion of an ICU. When somebody is going south, you're not worried about putting anything into the medical record. You're just worried about taking care of the patient. Get the Pixis open and give me the drugs I need, okay? So I don't think there's a lot of experience out -- worry about

RiskMAPs within that area. But we need to remember that this is not just a free lunch when we do hard stops, okay?

There's another option. Let's use carrots, okay. Let's not do all this tough stuff and stop everybody. Let's make -- do the right thing because you're going to get paid more. We heard about pay-for-performance earlier today. So you can put in soft stops, that we can increase the reimbursement if you do the right thing. So Aetna tried to do this on the east coast. They had never did it where I was. I was always asked them if they would because I would be glad to take the extra reimbursement, but they never offered it.

What we know is the depression care is pretty poor across the country, really across all the avenues, and it may not just be totally physician issues here. There's a lot of different issues around how depression is diagnosed. But just leave it to say, it's pretty poor. We know if you PHQ-9 monitoring, which is a simple -- it's actually 10 questions, but it's called the 9 -- actually

it's 10 questions, and you respond to them in a very organized fashion that you can improve depression management markedly, okay? This study was done by a good friend. His name's Bob - never mind. Was very, very well done.

So they said, well, this is pretty smart. We'll pay you extra if you'll tell us you'll use a PHQ-9 and use it on a regular basis; we'll pay you extra for every depression visit. Except to make sure you're doing it right, you had to go online and do required web training, and here's the extra strap in your billing. When doctors looked at that, and they looked at the $1.50 or whatever it was extra they were getting for a visit, and they said right, okay? That does not compute, and so nobody used it.

So I think we've already heard this. I'm going to go through this one really fast. But it works. It has to be built into the work flow. We've heard this one already. Easier to make the correct action than the wrong

action. Classic one that Peter talked about, as soon as you see that you ordered this medication, it sets up the next lab test to be done. It says does this lab test in six months. I'll put it in here, and if you don't have it done, it'll flash a warning or send your patient a letter to let you know. You have to have robust data scavenging and robust algorithms. You cannot just think -- this is not a 90 percent solution even, okay? You must take into account all the outliers or you will get people abandoning it. So that means you must sweat the small stuff.

Is there small stuff in RiskMAPs? Well, let's take Accutane, isotretinoin. We've been talking about that one a lot today. It's certainly the one that primary care physicians will use the most. We know at Kaiser, 90 percent of people are dermatologists. But you know what? When you get out to the real world, out to those red areas, there's not a lot of dermatologists out there, okay? So that becomes me that's doing that. So we know all about this part of it.

Are there exceptions allowed in the iPLEDGE system? Can I tell you that this person may be 32, but she's already had a hysterectomy, therefore I can't do it, okay? What do you do with andogen insensitivity syndromes? Should we be doing pregnancy tests on Turner's or not? Turner's syndrome has some chance, but almost, you know, till you get pregnant. Does that person have to be on two forms of birth control that makes her sick to get this?

By the way, which clinician handles both of these issues? And the problem is you not only need to make sure you have an negative pregnancy test, but you got to keep counseling about birth control to this person. Gosh, the last time I looked, dermatologists did not do a lot of birth control counseling, okay? In fact, as I think about it, I'm probably the only physician along with David that our group -- that actually does both of these things routinely in my practice every day. So where do you want this happening? I think it's a tough question.

Avoid "steering by the wake." Steering by the wake is a way to keep a boat very straight, okay? If you're out there in the middle of the ocean, you can't see anything. You have no markers, okay. If you don't have a compass to tell you where to go, you look behind you. As soon as you make a move from one direction to another, you're wake will tell you. But if you're looking behind the entire time, you know what? You run into the iceberg that's sitting in front, okay? So it's a great way to stay on track, but you have to be careful about it, okay?

Some misconceptions here. We heard earlier that 3 percent of physicians in this country are using electronic medical records. Well, the latest survey of family physicians says 40 percent of us are now using electronic medical records in this country. We use E-prescribing. We may not like that it works very well right now, but we use it, okay? There are data standards already developed to transmit data, okay? The quality of care record is in fact a lot easier system to use in HL-7.

It works in primary care standards. It's XML, which you can look up if you need to. It's called Extensible Markup Language. It's a quick language. I can take and give my patient a CCR record onto their hard drive -- or onto their little thumb drive. Exactly how we got our slides here today. I can walk into any doctor's office, and if they don't have a way to read it, you can download a free reader from the Internet in about 30 seconds. An entire medical record comes up. So (indiscernible) committee thought the FCCR was something that really needs to be explored. I understand that pharmacy is now talking about interfacing with the CCR.

Personal health records, okay? We have a lot of stuff -- there's been over a 110, maybe 150 regional health information systems that have sprung up in this country in the last five years. And I think at least half of them have now died out already, okay? AHRQ has spent a lot of money working on this. I know because I worked on one of their multiple million dollar grants on this area.

I think it may be an area that time has already come and gone.

I think that what we're going to end up doing more likely is we're going to give people their own records, or let them have a place to store it, even if they don't even want it -- use it themselves. I'm going to give you a place in the Internet, we'll put your data out there. You're in control of it. You tell who gets it. It's your's. You can manage it if you want. You can just let your providers manage it if you don't want. But we're not going to spend all the infrastructure to do all this ourselves. Things for you to think about.

Rx Hub is very big I think on the east coast. We don't have it in Colorado, but it's another way you can move data around. Right now they're just moving the medical -- mainly prescription data. But it's not very hard once you get all the connections together between my office and that pharmacy to add in a lab piece of data if we need to.

The biggest issue I think right now is to make sure that pharmacy receptor sites and clinician and messages and our receptor sites are to talk to each other. The edit systems that we hear about for pharmacists, they're very much -- they're usually talking pharmacist to pharmacy benefits management systems, and they don't talk the same language we talk at all, okay? We cannot connect them. It's not hard to do if you just start talking about it, and that's what Rx Hub is doing commercially, but it needs to happen on a bigger level than that.

The last couple of things I want to talk about is evaluation. We hear a lot -- if you're in the NIH part of the world like I am, you hear a lot about the phases of translations, Phase I and Phase II. Phase I kind of takes you from the molecular side of it, and the ideas to an animal or something and maybe you'll get to a person. And then eventually you move it on out.

But we really talk about -- this is a paper from one of my colleagues in Colorado called the "Blue Highways

of the NIH Roadmap." And that is that there really is another phase that goes on. We call it Phase III, way out here. And that once you get your guidelines together, once you get your RiskMAP concept in place, okay, that's great. It's now ready perhaps for people, but it's not ready for practices. It's never been tested in a practice environment. And then until you do that, you're really not clear what's going to happen when you roll it out.

Take the asthma guidelines, take CPOE, take prescription writing. You really have to do that last stage of testing, and you really have to take it out to your clinicians, and you've got to take it out to (indiscernible). What happens in the VA is very different than what happens in a rural physician's office in Holyoke, Colorado. You need to be studying all of those areas, okay?

So I'm under coal. Coal's real common. Diamonds pretty rare. RiskMAPs, you know, you think about these as kind of the diamonds out there in some ways. You

know they're pretty rare. Primary care probably doesn't matter very much how many of them we use. I think that creates a lot of pressure to not really rethink this system a lot, okay?

And I would like -- I'd like to think about a couple of different things. Pharmacogenetics, okay. Well, when we start rolling into pharmacogenetics, the issues of RiskMAPs I think will totally change. We're going to have the issues of drugs that work great for Person A and kill Person B, okay? And we darn well better get it right, okay?

I'm hopeful that we can think about RiskMAPs as a driving force to look at the rest of the system. Let's make it easier to do good RiskMAPs. If it becomes easier to prescribe Accutane such that I can get the data from my office to the pharmacist, then I can do that for any other drug I want. And that becomes safer for everybody, not just for this one single drug. So let's use the system to drive the entire system as opposed to trying to solve a

small problem.

Some hypothetical's. You know you got a drug that raises HDL and should lower cardiovascular risks. Anybody heard about this drug? You know what? They kill people. But maybe it killed people of certain types than not. Who knows? We haven't gotten the genetics on this particular issue. These are hypothetical's really. I don't mean to talk about them.

But dramatically improves the function of individuals with schizophrenia but increases the risk of culminate hepatitis. These kind of drugs right now are typically pulled from the market. I believe in the future, we're going to start seeing a ton of genetic work done on these to decide whether they're some sub-class of people that actually have the effect you want.

What does that mean? That means we have a whole other data storage problem. That works well in this country. Does anybody remember the universal medical ID for HIPAA? Mm-huh, that went over great, didn't it?

Okay. Now we're not going to take just a little ID test that's going to identifies you, but we're going to take your entire DNA sequence and we're going to stick it someplace where everybody can get to it. Take your (indiscernible) blood. Run it, put it into a bank, and we'll all just prescribe against that. I am afraid that may not work.

I guess my point is that we have a fragmented system. The fragmented approaches aren't going to solve where we're headed, and we're going to have to think of different ways. And I really would like to think of the RiskMAP system as a way to start thinking about these. How can we put some effort into solving our bigger problems? They really are here.

Forty percent of my colleagues have their data electronically already. They can transmit electronically wherever you want that data. If you bill Medicaid in most states, which most of my colleagues still do, you bill electronically. You're already transmitting information,

okay. By the way, I know Blue Cross, Blue Shield in New Jersey is passing information back to their primary care providers taking their pharmacy benefits data and making sure they get it back. So starting to deal with two-way streets. I think this is where we need to be dealing. Thank you very much.

DR. MEYERS: I'm going to invite the other panelists to join us. Does anybody have a clarifying question for Dr. Pace? We do. Would you just identify yourself, please?

MS. KRAMER: Judy Kramer from Duke University, sir. Can you just clarify -- I heard you say that the personal health record -- that you thought the time might have come and gone, and I didn't really catch your --

DR. PACE: I'm sorry. I was talking about the RHIE's that are out there, the Regional Health Information Exchanges.

MS. KRAMER: Oh.

DR. PACE: Okay. So I mean the classic ones of

course are the one in Indianapolis and the one in Santa Barbara. There's others around. They are basically where you put in things like ed servers, and you have the hospitals and the clinicians all sharing their data through complex algorithms or who gets access to what. And they're great when they work, but they're very expensive to maintain. And I think the way we're going to do that is we're just going to say here, patient, put your data up on the website, carry it around with you on your thumb drive, how do you want to access it, and then you release it to whoever you want to when you want to.

MS. KRAMER: Okay, so you're actually favoring the --

DR. PACE: I think that's where we're headed. I think personal health, right. I mean let's face it, we've got Google, WalMart, IBM, Hewlett Packard, everybody billing their own PHR's right now. I'd hate to go against those.

DR. MEYERS: Okay, so we're at the point in our

presentation where we've had four really I think fascinating presentations on different perspectives on how payers and providers think about RiskMAPs. I'd like to ask everybody to stand up and stretch. And as you're standing, think do you have a question that you'd like to pose to one or all of our panelists. And if so, start lining up behind the two different microphones because we do need those to be heard by everyone. Okay, if folks can start taking their seats, we'll see who's at the mikes.

And again, what we're going to try to do -- we'll start with a group of questions from the audience, and then we'll leave the panel. I'm going to type those up. If the panelists want to jot your own notes because you might not be able to see them as well. But I'll read them to you if you have questions, okay? And we'll just alternate mikes. I'll start on my right. We're going to get them all so it doesn't matter. Just introduce yourself.

MR. LILIENFELD: David Lilienfeld, Fibrogen.

One of the things I was struck by is the contrast which wasn't really commented on between the closed systems, like Kaiser, the VA, and like -- and the open systems of the solo practitioner or maybe in a group practice in terms of dealing with clinical data and the impact of HIPAA and the ability to move data around. Not just in terms of by the practitioner but by somebody else and getting access to those data.

Because one of the things that I think has come up in terms of the pharmaco-epidemiologist trying to get a handle on either an adverse event profile, or perhaps trying to design a risk management program is the lack of accessibility of data that's really very key to being able to design a program that makes sense, that has some clinical relevance that fits in with the way in which the healthcare system or systems, which will probably be a better way of putting it, operates in this country. And it's just something that's very striking.

When you talk about a closed system, the data

are all there. When you get outside of that, try dealing with the system in terms of HIPAA and the misunderstandings that go on. It is a very challenging situation.

DR. MEYERS: Great, thank you. On the left.

MS. BLACKWELL: My question is really asking the panelists to comment on actually wearing my pediatrician hat now that this is a gaping hole of attention in terms of -- you talk about a personal health record. Well, then of course you're talking about parents having a personal health record. Well, I worked in the Boston Medical Center actually, which is a very, you know, needy population where having parents have a personal health record for themselves is a questionable idea, and having them have it for their children is a guaranteed recipe for disaster.

And you know, all of these systems for RiskMAPs and information access and payers and things really need to consider this large special sub-category of people.

And I really want people not to forget about the children.

DR. MEYERS: Thank you. Please identify yourself.

MR. KAPLAN: I'm David Kaplan. I have four quick points if I may. And they're somewhat Tysabri centered, but feel free to broaden your responses. Dr. Flamm, you said sometimes you require failure of the less risky drug before approval of a RiskMAP drug. Do you consider differences in efficacy as part of the overall assessment of risk versus benefit?

Also you talked about comparative effectiveness information. I think we would all probably agree that head to head trials would be best, but generally the drug companies aren't that motivated to spend that time and money. What sort of lower threshold might be appropriate?

For the three of you from these large plans, I was interested in your approach to Tysabri as possibly differing from the TOUCH program because I found that some insurance companies are requiring failure of one or two or

three of the older drugs and define failure differently, that sort of thing.

And the last point, electronic prescribing, I'd love to be able to go into my doctor -- I go to Georgetown Hospital, and they write prescriptions on little pieces of papers that I then have to drive over to my pharmacy and drop off and either wait around or -- what can we as consumers do to push our physicians to do electronic prescribing, and in fact go beyond that to these personal health records? And then if we have personal health records, how do we get our doctors to update them appropriately? Thank you.

DR. MEYERS: Thank you.

MS. BLOOM: Cheryl Bloom. I have a question for Dr. Flamm also regarding Tysabri and would like her to elaborate more on the approval process through Blue Cross, Blue Shield, BCBS, on the approval process. I've had many questions from patients regarding the maize that they are put through on getting the drug approved and the prior

approval process, our prior authorization process, and it is extremely cumbersome. And because of the billing codes and not knowing what to do, and some of them have just frankly given up. So if you could address that, I would certainly appreciate it. Thank you.

DR. KWEDER: Sandra Kweder from FDA. I have a question for all of -- anyone on the group actually. As we look at these, trying to put together programs that balance ways to potentially mitigate risk and inform with not over-limiting access to medicines, I would say the biggest -- the most vocal critics and biggest push-back that we got is from healthcare providers.

I mean my e-mail box, when there's a new risk management program that comes out -- and I would say that is despite in many cases really extraordinary efforts by mostly the companies to inform everyone -- inform not in every case but in many cases months in advance what's coming and how to interface with it.

You guys are in a unique position because you

hold, most of you, have some purse strings attached to, you know, your ability to prescribe. Certainly not you. But I guess a question that I have for you is what can be done to better engage the provider community in making these programs manageable. Here's one -- I mean there's always going to be some difficulties because they're not business -- they're not today, hopefully somebody -- business as usual.

MS. SMITH: Meredith Smith from Purdue Pharma, Stanford, Connecticut. This is a takeoff from a comment or point that Peter Glassman made, but it's really directed towards all the panelists there. And it's in regard to efforts to manage the risk associated with opiates and other drugs that have abuse liability. I'd love to hear about policies, initiatives either in place currently or under consideration that indicate some efforts coordinate or collaborate or build on existing RiskMAPs that sponsors have developed.

MR. MILIBUSLY: Hi, Kevin Milibusky (phonetic)

and from Santa Fe Adventis. I'm just following up on a comment from David. It's not a Tysabri, eccentric question, but a more global question. I'd like to hear more along the algorithms and the line of thinking with Blue Cross, Blue Shield since you're the only representative up there for the provider.

What is the thinking -- explain to me a little bit more the thinking that goes along, or the algorithm that's used when you're considering new drugs to go on a formulary versus old drugs. And I know you alluded to it earlier. But, you know, we're in an environment for whatever reason FDA doesn't seem to enjoy being called before Congress, so therefore they seem to becoming more and more risk averse. And we're in an environment now where more and more drug compounds that are being developed have new mechanisms of action, have less and less safety associated with them. So the likelihood of having greater RiskMAP programs associated with them is going to increase.

And I would hate to get into a situation -- maybe we're there, maybe we're not -- but I would hate to be in a situation where providers are only looking at whether or not a program compound has a RiskMAP associated with it versus a compound that may be a little older, may be less efficacious, but not have a RiskMAP associated with it and require that product to be considered first. So it's really a complex question looking at safety and efficacy, new drugs versus old drug and RiskMAP versus no RiskMAP, given the current regulatory environment that we're in. And that's not only within the U.S. It's a global, risk adverse environment that we're in.

DR. MEYERS: Thank you.

MR. KAHN: Sidney Kahn, Pharmaco-Vigilance and Risk Management, Inc. First some encouraging news that Dr. Pace might like to know about. I just learned that in the UK, GP's pay has been raised to the region of 150,000 pounds a year, which is pretty impressive. So I hope that doesn't start a reverse brain drain, but anyway. I

actually have a question --

DR. PACE: The surgeons don't make as much either.

MR. KAHN: I also get free healthcare provider as well. I actually have a question. And the FDA's position is that the FDA approved labeling is to (indiscernible) RiskMAP tool for all products on the market. But in clinical decisions, support systems, and particularly those relating to a (indiscernible) describing, it's my understanding that quite a substantial amount of the information that is used as the evidence base for those systems is actually not the label itself but rather some extract distillation or compilation of information from the label and elsewhere.

And given that -- and if that is the case, which I believe is certainly the case in the program I participate in, how does that tie into FDA's risk mitigation activities when the providers of the evidence base for the support systems are actually putting

something different in it?

DR. MEYERS: Okay, and this will be our final question for our first round.

MR. GANGNON: Mine is similar to that. I heard Carole Redding --

DR. MEYERS: Could you --

MR. GAGNON: I'm sorry Jean Paul Gagnon from (Indiscernible). I heard Carole Redding say to you that under use of the RiskMAP, the starting point is in some cases it's adopted. And then later on she said plans can use elements of the RiskMAP. And then with Peter Glassman, the VA, I think he said each VA does its own thing too. And I guess my question is how can a company working with FDA who develops a RiskMAP, how can that RiskMAP be effective if every plan deals with it in its on way and changes it around from what it was agreed upon with FDA and the company?

DR. MEYERS: Okay. So summarizing from what I heard, a lot of -- and for those of us here, you can keep

score and see how we're doing on it, if I got your question close to what I heard. Carole, there were at least a few people who specifically wanted to follow up with you on your presentation. And then there were some broader questions for the group. And starting with the last one, from your perspectives of both large and small health systems, recognizing that doctor's offices are in a sense their own systems, how does the large manufacturer working with the central federal FDA agree it's one program if we're going to all interpret it differently? And is there value in that? What are the challenges of that? Are there systems that allow for both that central and that customization to think about that?

And that leads into a larger question that I just want to underline, taking a moderator prerogative. From your individual perspectives, what are the policy options for us as a community from each our different perspectives as a nation moving forward for safety? What are the policy options we have in terms of RiskMAP to meet

the needs of your particular constituents? And with that, I was going to again ask Carole to start, and then the rest of you to just jump in on any of those that you heard that you would like to respond to.

DR. FLAMM: Well, I can hear from the series of questions that this issue certainly strikes a cord, and I can appreciate that.

I do need to say several things in that I work at the Blue Cross, Blue Shield Association which is not one of our health plans. And that these types of decisions are made plan by plan, and there will be differences that each, you know, plan experiences in the process. So I'm afraid I can't really answer your question with regard to the operations and implementation issues, but I can appreciate with compassion the difficulties and sort of navigating through those administrative processes. I think I'll take this back as sort of some comment to our pharmacists that these were some questions and some concerns raised. But I do

apologize that I don't think I'm in a position to be able to really answer your questions specifically.

In terms of the questions around whether efficacy and safety are both taken into consideration, I do think that is fair to say that certainly the balance of comparative efficacy, given the information that may or may not be available to make those comparisons, is taken into consideration that those decisions are made in careful consideration of those clinical issues as well as can be determined on a population basis.

DR. MEYERS: Do any of the other panelists want to talk about that issue of how do we balance safety and efficacy, new versus old?

MR. GLASSMAN: I think one has to be very careful when we're throwing those things out. I mean we hear a lot of things like new drug, somehow it gets always associated with greater efficacy. This is clearly not true. And to continue to say that is to do an injustice I think to a lot of the older drugs, and it's not evidence based.

Of course, we take it both into consideration. You have to. You also take into other things as well, but that's always the case. In many cases, new drugs don't have good evidence as to what their level of effectiveness or efficacy is going to be, so you either have to make some assumptions, not always a very good thing to do, or you have to wait for a great amount of data. Tysabri, for example, it came up a number of times. It is a work in progress. It's been withdrawn from the market once, or at

least held from the market once.

I have concerns. As a pharmacy benefits manager, I personally –- I'm speaking for myself now –- I have concerns about this drug. Whether they'll play out in the long run or not, I don't know. But I think one has to take into –- these things weigh heavily on me personally when I make decisions on this. On one hand I need to figure out how to get a drug out there to people who really need it. On the other hand, I have to be mindful of the fact that drugs sometimes don't do what they're supposed to do. And it may turn out –- unfortunately we may find that out later. So, yes, of course, we take that into consideration, but it has to be done in a very concerted, careful, thoughtful manner and looking at the existing evidence when you make such decisions.

DR. PACE: This whole area was a huge area for the IOM Committee. It was very difficult for us to deal with the issue of whether an AED, for instance, was in

error or not when you don't really even know how drugs usually do respond in various populations. You don't even know the dosage that necessarily makes sense.

Kids, children are a huge issue. I think probably a majority of drugs used in children are used off label because studies have never been done in children. They're starting to get better. Certainly do the databases that we work on needs to be expanded. Comparative studies are very important.

I think that there's a chance we could figure out how to get more in of one trials just to use them clinically and extract that database. You might have a better way to deal with some comparative information, but lots of ways we need to rethink this a little bit to get better information to be able to make our decisions. Questions.

DR. MEYERS: Wilson, you said NM-1 trials. For those who don't know, can you just quickly say what that is?

DR. PACE: An MN-1 trial is you really use it for chronic disease issues primarily, but it's where you use the patient as their own control. And you can do an NM-1 trial between drug A and drug B, between placebo and drug A, or between two doses of the same drug. And as long as you have a careful monitoring system, you can tell very clearly what is drug related and what not down to –- and when you (indiscernible) a population based information –- there was a nice paper done in –- a theoretical paper done in 1999 sponsored by AHRQ that talked about the potential of using NM-1 trials at the population level. The power is about 10 times as high. And so I really –- you know, it's an area we need to consider as how we can get better data quicker from smaller populations.

MS. BLACKWELL: (Inaudible).

DR. MEYER: So the speaker from the audience, your name? Mary Blackwell's comment was that RCT's are very problematic, especially from a pediatric point of

view. That they can be ethically difficult to do as well as prohibitive in other ways. And that we need –-

MS. BLACKWELL: (Inaudible).

DR. MEYER: So we need to develop new methods to understand how medications work in the children population.

MS. BLACKWELL: (Inaudible).

DR. MEYER: Right. Okay.

DR. GLASSMAN: I would comment on one thing on comparative efficacy studies or effectiveness. Sometimes they can actually help define the questions, define what we know and what we don't know. And that actually can be very helpful in putting it down carefully on what we do know. It doesn't answer everything, but it can answer some questions in the absence of –- obviously head to head RCT's. Even head to head RCT's don't always answer the question either. That's another question. That's an unfortunate thing. So when we answer one question, we always end up having to ask another one or two questions

after that. But it can help define the more global picture.

DR. MEYERS: So from the panel's perspective, we were interested today in talking about what can the FDA learn from what providers and payers are doing. The FDA threw back to this panel to say what can the FDA learn about how do we engage more effectively with these two communities. Are there simple things or more complex things that you want to talk about how RiskMAPs can built with and communicated to the payer and the clinician communities?

DR. PACE: I'll start with one area. I think that any time that you're taking most of the drugs you currently you put on RiskMAP activities and say that a letter or any kind of information is going to really hit my brain very much as a primary care provider at least. Forget it, okay. This is just so infrequent.

First, a rare event. You're talking about presenting a rare event, preventing a rare event that most

of us are never going to see in our life, even if the RiskMAP doesn't exist, okay? So therefore, it doesn't rise to the level of importance for today, and I'm an adult learner, okay? Adult learners pay attention to what you need right now. They don't learn just for the sake of learning. So we're going to need systems.

You're going to need very, very different approaches to deal with this if you move outside of drugs that are used commonly in certain –- so if a dermatologist may use Accutane often enough, it makes bigger sense for them. So you're going to have to limit access, and we're going to have to find systematic approaches. Some of the closed systems have done it.

What I've tried to present is that it doesn't mean today that we have to give up on the primary care community that's not in a closed system. But we need to have pushed across the system as it's happening to start communicating. It's all about communication and then making it happen. I could talk about THR some time, but

don’t know if we need to get into that one right now.

DR. MEYERS: And Carole, you had a point in your take-home, didn’t you, on what the payers were looking for?

DR. FLAMM: Well, I think that –- one of the question’s points of we shouldn’t necessarily have people inventing the RiskMAPs over and over again. I think the themes on what they’re requiring makes sense to have some simplification alignment around that. The ways in which they’re administratively executed may be what’s, you know, more opportunity to be flexible. So trying to fit it in with your existing system to reach the same goals, to sort of align with what the requirements are makes some sense. We wouldn’t want to be in the position of having to reinvent those RiskMAPs over and over again. So having it well done once is helpful.

DR. MEYERS: Dick.

MR. WAGNER: One of the –- and again Tysabri’s a good example. One of the most difficult things is I have

not been successful in actually getting a RiskMAP. Most of the drug companies will say that they're proprietary. If you want them for you, FDA, you'll get a redacted version.

And I'm thinking to myself, well, why should something be so hidden if it really has a lot of value? And I know they may be proprietary or other intellectual property in there, but you're not going to get a lot of buy-in until we can actually see the thing. And I mean someone –- I was telling someone about I was coming here to do this presentation, and I said that I kind of think like Ronald Reagan trust but verify. They said, well, actually, you know, you can't even say about the drug companies. We don't trust them and we do need to verify them.

And that's just the way things are. I mean I don't want to get too agitated, but we got to see what, you know, the original source document is. It's like looking at peer review literature.

The drug companies are under a lot of pressure to sell product, and it's just the way it is. But when they come and talk to us, we say, you know, we're always interested in hearing your sales presentation, but you know what? I want to see what the New England Journal of Medicine article is, and we want to do our own review, make our own decisions.

So I think one way to get more credibility in the RiskMAP program, first of all, there's some education because that term is not well recognized. But we've got to see the original RiskMAP. We've got to see what the FDA and the company have agreed to and make our own decisions. I think if you do that, it goes back to how care management and disease management's worked in this country. It's not very successful and things are going to top down and impose on physicians, but it works a lot better when it comes from the bottom up and it's kind of growing.

So, yes, standards of therapy. It's really easy

to get people engaged around the high quality of we want to do the best we can for our patients, but don't tell us how to do it today in Kaiser because it's going to be different than rural Colorado or at the VA.

But I think we can agree to try to hit the standards of therapy, standards of quality, standards of safety, and then give us some flexibility around that. So I would actually put a challenge on it. I think we're going to have a presentation later. Why can't we see the RiskMAPs? I think the RiskMAPs got to be disclosed to the folks who are paying or providing care. And I think then if you can engage that group, you're going to have a lot more success at getting that fully implemented and have buy-in and support to make it a more safe system, to tell you the truth.

DR. MEYERS: Peter.

MR. GLASSMAN: Yeah, I think Sandra asked the question about how do you get people more engaged. One of the things we've done in the VA is we send out these

documents in a variety of different ways to make them available for people to comment on. And, you know, there'll be like a two week turnaround or a four-week turnaround, one week, or whatever it might be. And so one of the things you might want to do is over time try to develop groups that you can talk to about these RiskMAPs, so if it was a neurological drugs, maybe there are a number of neurologists who would sign up to be willing to get the RiskMAPs and talk to them in the draft form that they can then comment –- send you back comments as to what might happen in their practices, or if it's a pediatric drug.

Or you may just need a core group. It may not a huge group, but maybe at least it will be representative, people who are interested in such things and can speak from the point of view of the providers. We sometimes get only a few comments, and sometimes we get a lot of comments. So that might be a way to start bringing desperate communities to hear what they have to say and

then taking that into account as you send these RiskMAPs out in its more final form.

DR. MEYERS: I'm just going to jump in and say something I heard here is that when you're working with communities who don't yet have trust, that the FDA could serve a role as the broker here, the honest broker, to bring the manufacturers, the distributors, the prescribers, the consumers, so they're all being heard and hearing each other. And that would reflect I think well in what our panel said as a need that isn't yet being made.

DR. PACE: One of things that I hope's going on since AHRQ and FDA are both here together today is that –- is hopefully will know there is a task order out right now to form one to four networks of databases that have never been connected. Now most of us, through the design mechanism that was mentioned at the beginning of this whole day, and those of us still working on those, I think most of us think that means bringing clinical data to bear

on drug problems.

And so I'm hopeful that whoever gets those, and I've love to be one of them, will be talking between these two agencies because that's the kind of thing we start to see is that those become the people you're talking about. Outside of the closed system, potentially those become clinicians who are dedicated to trying to look at this further and answer those questions.

DR. MEYERS: All right, we have a few minutes left, and there are a few more things we could possibly touch on. But I want to turn it back to the audience. Do folks have comments that they wanted to add to this panel, or any new questions that were raised by what you've heard so far? Again I do need to ask folks to go to the mike for this.

DR. PACE: While people are going to the mikes, there was a question about clinical decision, support and labels. And I think the information that comes out of the companies that do clinical decisions support work is far

beyond what's in a manufacturing label because they deal with the non-approved use of drugs as well.

Unfortunately the database again is poor, and they tend to be just as risk averse everybody else. So once anything has been described, even if it's been later taken away saying this is really not real, it continues in the databases forever. And I can show you over and over again in our's. So it really needs a central work to get that –- to get this –-

The key important side effects that really make a difference that you really want to avoid, not just for RiskMAP drugs, but for all drugs, we need to figure out how to get that core knowledge together and make sure that it's in all of EHR's, not variable.

DR. MEYERS: Thank you. Okay, these final two comments?

VOICE: Just a follow-up question to your comment about RiskMAPs. In the case –- I'm interested in knowing what kind of information you're looking for on the

RiskMAP because in many cases that's part of the approved product labeling. And I know it's certainly is for Lotronex. There's a bit of detail in there on the RiskMAPs. So what is it that's missing from your perspective?

MR. WAGNER: From my Kaiser perspective?

VOICE: Yes.

DR. MEYERS: Hold the phone.

MS. BLOOM: I have a follow-up on that as well. During my talk, I commented on not being able to show slides of the patient enrollment form and the TOUCH pre-infusion checklist because it was considered proprietary information. And I was not able to get the information from Biogen to show because it just was not available. So that was part of the RiskMAP procedures, and it was just something that I could not have and was not able to show it here today. So I agree totally with your comment.

MR. WAGNER: I don't have –- specifically we picked on Tysabri, but I think it's in general. I haven't

seen any RiskMAP myself. So I'm wondering why can't I see those RiskMAPs. I'm not even sure what's in those things.

But what's really troublesome is when folks come in and try to sell us on these closed systems and they tell us how to behave. And we have to treat our patients in a certain way, and we have to send forms to their folks who are going to review it. It doesn't fit with how we practice medicine within Kaiser Permanente, so I'm talking more from my physician colleagues' standpoint. And the neurologists are going you know what? We will have high standards. We will exceed or meet the standards in the community. We can agree on that, but I don't need folks to tell me every single step that I have to take every day to manage his patient because I somehow manage these patients very well without this. So, yes, let me demonstrate that I hit quality, but don't come in and really disrupt what we're doing in terms of patient care, the infusion center, the people that work in there, the documentation that flows. It doesn't seem to add any

value from our perspective.

It may be different outside of a closed system because I can aggregate data. And I was trying to think about this. What's the Lilly drug for substance in the hospital setting? Can you remember? Yeah. I can't even think of it. I don't think we use it anymore. But you know when that drug first came out, had lots of risk drain-offs involved. For 30 hospitals in California, we collected the data for about 18 months. You know what? A lot of patients died of that drug. And I just had to share the data back with the physicians, the ID physicians, other physicians in the hospital settings. You know what? We made our own decision. That drug was too risky in general to use. I didn't have to deny any patient or have prior authorization. The data said very difficult to use correctly in a real hospital setting. And it turns out we're not using that drug anymore.

So I would do the same thing with Tysabri. Have to collect that data, aggregate it across several centers

where neurologists practice. And over time, we'll actually figure out does this drug actually make sense for patients, and where does it fit in, and what is the risk profile for this drug, and how do we continue to incrementally better manage that drug for those patients that really need Tysabri for MS versus the other therapeutic options that they have on the market.

DR. PACE: So as an example, there are other issues around this RiskMAP issue. I actually gave up being on the iPLEDGE system because I don't see patients often enough anymore. But out of 14 clinicians in our primary care clinicians in my office, two of them have elected to be on the iPLEDGE system. And we're all paid salaries. But they recognize that every time a patient comes in for prescribing that drug, that's a 40 minute appointment. You can't –- I mean all I'm doing is refilling the prescription for 30 days. That would be a five minute visit for most things. That's a 40 minute appointment.

And then they tell me about a third of the time, they end up making up the data because it's one day outside of range. Nobody will tell you what those ranges are very easily on the site. It's hard to tell, but your pregnancy test is one day out. Well, you know, that doesn't really fit with either the schedule for the patient, the schedule for the doctor. If it's too long, I guess I can understand that, but if it's one day too short. I'm not quite clear what the risk is in that sense, you know. You're only going to give the next 30 days.

So it's that kind of issues that it's difficult to pick up on the site, it's difficult to figure out. People have to put it in multiple times. And I can tell you that they tell me that I finally just end up fudging the date so I can get the person their medication.

DR. MEYERS: Okay. We've got about four minutes. So what I was going to do is ask each –- give you each a last minute. Just from your experience, what's

working, what's not working, what do you want to leave here with people knowing. Give you a few seconds to think about it.

(Pause.)

MR. GLASSMAN: I think the one thing that we've probably learned over time, you know, obviously people are going to have differences of opinion and differences of approaches. But the one thing I think we've learned over time is communication, open, transparent communication about these issues I think moves everybody ahead in the long run. And even with disagreements, you can work through those and I think come out ahead.

The one thing I would highlight is to continue to communicate about these issues across plans, within plans, across plans, within agencies, across agencies. I think that's probably the lone message that I think would be a good one to leave with.

DR. FLAMM: Also along those lines, I think that we would strongly support increased transparency, and

information is the basis that we need to build our systems around. And then look at ourselves as collaborative stakeholders trying to work together for a common goal to protect the safety and improve outcomes in terms of quality and efficacy.

And hopefully to take the date that we all have from our different environments, HIPAA restrictions to be considered, but figure out how we can learn from increasingly bringing our data together to evaluate what we're doing and what we can do better.

MR. WAGNER: I've already mentioned that I think the flexibility around procedural things and system things that are closed systems certainly have some flexibility around implementation. A requirement that if that happens, closed systems have to meet or exceed the standards, that data should be available for review by appropriate oversight boards. Eventually it should be published in the peer review literature so that people can actually say it is transparent, it is good quality. And

it’s actually then allowing people to use those procedural advantages or innovations to actually push the envelope, to actually provide more quality at a lower price because we’ll have some flexibility to do it smarter, less expensive and better and get credit for it too because there is a marketplace for healthcare in this country.

DR. PACE: And I would say that this is –- I know it’s a –- we’re a capitalist society and I happen to believe in all of that. But this may be one place where working together may in fact help us as opposed to being competitive about it.

Speaking for the private clinicians, if we can figure out a way to make this data centralized, such that once I have my interface with that system for my EHR, it doesn’t have to be redone every time another company comes up with the next RiskMAP. We’re talking the same information. You got a patient that needs some kind of monitoring, some kind of drug they shouldn’t be on. I mean it’s the same steps more or less to make things

happen correctly. If you can –- I think it’s a place you should be thinking about not doing this with a whole lot of centralized –- each person doing it, but think about putting it in one place so that we can all interface with it, and we can move this forward rapidly.

DR. MEYERS: Please join me in giving these folks a hand.

(Applause.)

(Break.)

(On the record - 3:15 p.m.)

MS. KWEDER: Okay, let’s begin. If anyone hasn’t noticed, there is a different time on every clock in the room. I’m going by the one straight ahead of me because that’s the one people at the podium can see.

Again for those of you who don’t remember when I asked the question, my name is Sandy Kweder. I’m from the Office of New Drugs at the FDA. And this panel is from the perspective of –- RiskMAPs from pharmacists and distributors perspectives.

Before I introduce the panel, though, I want to follow up on a point made in the last panel for point of clarification. I absolutely understand the frustration with not being able to see your RiskMAP, and some of the things that you've shared about your frustration of not being able to show pieces of working documents, I completely –- points well taken. I don't understand that myself. But just to clarify, most of the time when there is a RiskMAP, it doesn't come in a tidy little package that we could then say here it is. And that may be part of the reason that you feel like this is kind of a nebulous thing. And that's because these have evolved over the years and they aren't sort of a nebulous thing.

A RiskMAP may include the sum total of what the language is in a product package insert, plus the way the plan is going to –- the way the product is going to be marketed and people educated about it, plus certain forms that might go with enrollment, really depends a lot on the different products. But I think as the agency engages in

more and more of this, we'll start to see these taking a shape that better lends itself to the sort of transparency that we all think would be a good thing.

So with that behind me, let me just go on to Panel 3, pharmacists and distributors perspective. I think that there's probably no question why would we want to have a panel that asks pharmacists for their perspectives on RiskMAPs. But some of you may be wondering why distributors. And I hope that will become evident over the course of the panelists' presentations because we have realized that in many cases, the distributors play an enormous role in the success of any risk management program. We can spend all the amount of effort we want to educating prescribers, patients, pharmacists, you name it. But if particularly where there is a closed system, if the distributors are not engaged in participating, the whole program can go out the window in a flash. So that's one of the reasons we included distributors on this panel.

Lisa Bernstein is going to be your moderator for the panel. Lisa is a Pharm.D. and a J.D. She's been at the agency for a very short time. Almost as long as me. No, I'm being facetious. She's been at the agency for a number of years. She's one of our most experienced folks, and she holds the title of the director of the Office of Pharmacy Affairs, a very important position. Lisa.

MS. BERNSTEIN: Thank you, Sandy. This is a –- at least for me as a pharmacist and not a distributor –- sorry, Anita –- but I think that there's going to be some really interesting perspectives you'll hear from this panel. These are important stakeholders who implement the elements of the RiskMAP that enables access to the drugs, and they provide essential patient education for these drug products. And we've heard from a number of pharmacy organizations over the past several months that logistical implementation of many RiskMAPs has been –- particularly restricted distribution has been challenging to say the least.

And we also heard about challenges pharmacists have faced regarding medication guide distribution and dispensing. And FDA held a meeting about two weeks ago. We spent two full days just addressing the challenges regarding medication guides. So that's how big some of these challenges are for pharmacists. And if you are interested and you missed it, the transcript should be on our website very shortly so you can read all the exciting news from the two days that you missed.

For this panel, though, we've brought together various perspectives from different pharmacy practice settings, hospital, retail, managed care, and from the general pharmacist perspective, as well as from the distributors who are important in supplying the drugs to the pharmacies. And we could spend the next one and a half hours discussing the challenges and problems for these different perspectives, but they've agreed to help identify and recommend some solutions to overcome these challenges.

And on our panel today, we have Marcie Bough, who is director of Federal Regulatory Affairs at the American Pharmacists Association. We have Mark Gregory, who is vice president of Pharmacy and Government Relations for Kerr Drugs, who is representing the National Association of Chain Drug Stores, as well as the National Community Pharmacists Association. Nathan Thompson, who is director of Outpatient Pharmacy, Johns Hopkins Home Care Group, representing the American Society for Health System Pharmacists. Mary Ryan is vice president of the Pharmacy Regulatory Group of Medco Health System. She is representing the Academy of Managed Care Pharmacy. And Anita Ducca is director of Federal Relations?

MS. DUCCA: Regulatory Affairs.

MS. BERNSTEIN: Regulatory Affairs at the Healthcare Distribution Management Association. Marcie Bough is going to go first.

MS. BOUGH: Thank you. Again my name is Marcie Bough. I'm the director of Federal Regulatory Affairs

with the American Pharmacists Association. Very happy to be here. I'm a pharmacist and happy to be working with APHA, which was founded in 1852 as the American Pharmaceutical Association. And we represent over 60,000 pharmacists, pharmaceutical science, student pharmacists and pharmacy technicians and others interested in helping improving medication use and advancing patient care. APHA members provide care in a variety of settings, including community, pharmacies, hospitals, long-term care facilities, managed care organizations, hospice settings and the military.

My comments today will focus on general concepts and the need to develop system-based approach for risk management programs that are both effective in mitigating the risks and –- workable for pharmacists, physicians and patients. The agency must consider the need to balance the program efficiencies with pharmacists workflow and workload.

Given the growing number and variations of the

risk management programs, we can no longer address these risk management programs in a separate manner. We must look for consistency within the programs based on defined risk levels.

So what do we have with –- we have the prompt –- Foot Prompt risk management programs. We have challenges with the current risk management systems. Currently –- well, all drugs have a risk. There's no delineation within the prescription drug class to identify products that may have a higher risk, require more attention, or program registration. APHA recommends that the agency develop criteria to guide the determination of when drugs will be placed in a risk management program. The criteria would help create consistencies with the programs and help ensure that the proper products are placed in risk management programs, utilize a formal system for these programs, and assure that drug products are not placed unnecessarily within a risk management program.

Looking at the interventions and tools available

for risk management programs, we have a variety of risk management tools ranging between targeted education for the physicians or other prescribers, pharmacists and patients, participation agreements for the programs, patient screening, patient training and assessment, enhanced drug interaction screening, compliance documentation, and then finally process measures. Many of these we've heard in more detail earlier today.

Unfortunately pharmacists must deal with the confusing and –- pharmacists must deal and manage with the growing number of these tools and programs, each with different structures and often confusing requirements. This trends to focus pharmacists' interest and attention on administrative duties and often burdens rather than the appropriate medication use takes away that time that the pharmacist could be offering face-to-face medication therapy management to those patients to help manage their medications.

With the risk management program development,

the FDA currently uses a product by product approach. Programs may have a different and conflicting requirements in managing these multiple programs previously stated, focus the interest on the administrative burden as I previously stated. Whereas we've seen with the medication guide program last week, and in the efforts to advance the profession of pharmacy to focus time away from dispensing and towards that face to face interaction with the patient, we may see a greater value from these services, services ranging from the med guides all the way to risk management programs if we can help the pharmacists manage these programs and work efficiencies into the system to work with the patient.

With the program development, APHA recommends a system-based approach with use of standard tools based on the product's risk level. Each tool must have a consistent structure when used in any program. A system and appropriate tools should be identified now as we move forward so that programs can be evaluated both pre- and

post-implementation. Systems should have a common infrastructure and make use of available technology so that we're not recreating the wheel every time a new risk management program is implemented.

And finally evaluation of risk management programs. As we have heard earlier today and throughout these presentations, risk management programs must be evaluated at the practical level for both prescribers, pharmacists and patients. If so much effort goes into creating the risk management programs with great intentions, then equal effort must be used to evaluate the effectiveness of these programs both pre- and post-implementation.

Again with the evaluation measurements, there are things that should be included. Evaluations include actual health outcomes. With the use of these programs, documentation of patient knowledge and compliance with the programs and look at how the programs would work in actual pharmacy practice.

APHA also recommends that with the evaluation of these programs, the agency looks at the process to easily located risk management programs and have similar to some of the med guide recommendations, a single site whether it's Internet or hard copy of a place to summarize all of the risk management programs that are out there that's easily searchable and easy to locate so that any practicing pharmacist or other healthcare provider would be able to find what programs are out there for these specific products.

And I think what we've heard today similar to this that we also need a targeted educational campaign for the risk management programs, I think all of us in this room are aware of what a RiskMAP is. But I think we've heard from the patients and the people actually dealing with these programs that often those that are trying to implement them are those that may be the beneficiaries of these risk management programs aren't aware of them, have never heard of them, and some educational campaigns for

these programs would really help as we move forward.

In conclusion, pharmacists are prepared to and want to play a role, an important role, in their risk management. However, these programs must not be time intensive and not create undue burden on the practice of pharmacy. And they need to preserve the pharmacist's ability to provide patient care to the patient. Pharmacists help patients maximize the benefit and minimize the risk of their medications. And APHA would like to work with FDA and other stakeholders in developing a system-based approach to risk management programs. Again thank you for your time, and we look forward to working with all the stakeholders on this important issue. Thank you.

MR. GREGORY: Hi, I'm Mark Gregory, vice president of Pharmacy at Kerr Drug, 25 years in the pharmacy industry. Kerr Drug is a regional pharmacy chain in the Carolinas, about 102 pharmacies.

Today I'm speaking for NACDS and NCPA. If you

don’t know NACDS operates 37,000 community based retail pharmacies representing 200 companies. NACDS members are small, medium and large chain pharmacies, including traditional chains, like Kerr Drug, supermarket pharmacies, mass merchandise pharmacies, varying in size from four stores to over 6,000 pharmacies.

NCPA represents the pharmacy owners, managers and employees of more than 24,000 independent community pharmacies across the United States. So collectively there are about a total of 55,000 community pharmacies, chains and independents whose distribution processes are impacted by RiskMAPs.

Now Marcie’s theme is pretty much the same as mine because we wanted to talk about operational issues with implementing RiskMAPs. And really in today’s community pharmacies, it’s challenging to integrate the RiskMAPs into the drug distribution process, especially closed loop programs like clozapine and isotretinoin like we talked about earlier today.

The difference is really in the RiskMAP programs really present a barrier. A large part of the challenges is there is not a common design or platform, especially for performance linked access systems. Pharmacies are really well positioned to assist with risk minimization programs, whether the program includes education, reminders, or a controlled distribution program. But it's important to note that workflow standardization is an important component of filling prescriptions adequately and correctly. Current manual methods outside of the normal workflow and dispensing process interrupt pharmacy workflow and really can't compromise patient safety. So again we recommend the FDA needs to outline a more standardized process that can be integrated with an existing workflow to help ensure execution.

It's suggested, like others have suggested, to look at current pharmacy processes and technology such as real-time messaging, prescription claim, electronic adjudication, electronic prescribing, now recognized

medication management web-based applications, and existing learning management systems that are recognized in our industry today to be utilized, to facilitate and comply with RiskMAP requirements.

Currently drug manufacturers need a risk –- have a risk need to contract with firms to administer the risk management programs, which could be a conflict of interest. RiskMAPs should not be an opportunity for branding or a marketing advantage. The FDA should facilitate the selection of a central vendor. We propose that FDA contract with a selected vendor that all medications require a RiskMAP would utilize.

It’s critical that RiskMAPs are only put into place for medications that present a serious safety signal. This should not become the standard of practice. In the best interest of the patient, as long as retail community pharmacy can meet the criteria, the criteria of the risk minimization program, all pharmacies should be able to inventory and dispense the medications. Several

current RiskMAP programs restrict distribution and limit retail pharmacy access. Restricted distribution is not good for the patient and leads to fragmentation of care. The normal drug distribution and return logistics should be in place for these medications.

Patient counseling by a pharmacist is a critical component in the drug dispensing process. Pharmacists help to manage patients often complex medication therapies and positively impact outcomes. The pharmacist-patient relationship in counseling is an important part of the continuum of care. With the disparate risk management programs, this continuum of care may be interrupted. It was mentioned also earlier about flexibility. And really a continuum of care also can include a professional judgment that a pharmacy provider may make to allow an emergency supply of medication so therapy is not interrupted.

Pharmacists should be included in the group of healthcare providers that are reimbursed for their RiskMAP

consultative services. Currently there is RiskMAP programs that reimburse providers for pregnancy counseling. However, pharmacists are not recognized as a pay provider for this service. Pharmacists are very accessible and play an important role in patient care and such should be recognized and reimbursed as providers of consultive services related to RiskMAP programs.

Again dispensing a medication with a RiskMAP can be very time consuming process, and pharmacies are not currently compensated for the extra care and effort which includes up-front pharmacy staff training costs. Manufacturers or the payer community whose medications require extensive safety interventions should fund a system that in turn would provide compensation to the pharmacies and other providers.

There needs to be an increased level of cooperation and communication between stakeholders in the RiskMAP programs. A critical step in the design of a program should be understanding the system. All

stakeholders should be involved and invited to provide input during the design phase of a program well before implementation. Pharmacy providers must be represented on the RiskMAP team. Once designed, sufficient time needs to be allotted for communication to the pharmacies and training of staff.

A wide variety of communication and education vehicles exist in the pharmacy industry today, including channeling information through national and state pharmacy associations, utilizing the continuing education process, or developing web and conference call training and education. There are a number of learning management companies that are well recognized as quality organizations by the pharmacy industry.

And finally I might note that all record-keeping and reporting should be done electronically on a central system which would decrease the burden and interruption to workflow. Having one central vendor would help to drastically improve the efficiency and efficacy of RiskMAP

implementation, training, reporting and performance. And for one vendor to be accountable in facilitating stakeholder training, registration and communications.

Concluding comments include that the community pharmacy industry takes very seriously our role in drug dispensing and patient counseling for medications with RiskMAP programs. Pharmacy providers are well positioned to assist with risk surveys, risk minimization and pharmacovigilance programs. Extensive RiskMAP programs should not become a standard of practice. It must be limited only to medications that pose a serious safety risk.

So to some, we ask for all the reasons mentioned that FDA take into consideration standardizing processes and utilizing one centralized system for RiskMAP medications. Pharmacies also need a mechanism through the central system to be reimbursed for staff training, time and pharmacists' consultation services. NACDS and NCPA look forward to working with the FDA and key stakeholders

as they continue to work on RiskMAPs and their implementation. Thank you.

MR. THOMPSON: Good afternoon. My name is Nathan Thompson. I'm the director of Outpatient Pharmacy for the Johns Hopkins Home Care Group. I'm here to represent the views of the American Society of Health System Pharmacists.

ASHP is a professional association with over 30,000 members and represents pharmacists who practice in hospitals and organized health systems, including ambulatory care clinics, home care and long-term care settings. I appreciate the opportunity to present the views of ASHP on the implementation of risk management action plans.

ASHP's policies supports the current system of drug distribution in which prescribers and pharmacists exercise their professional responsibilities. The Society also acknowledges that there may be limited circumstances in which safety restrictions placed on the traditional

drug distribution system may be appropriate if the following principles are met. First, the requirements do not interfere with the continuity of care for the patient. Second, the requirements preserve the pharmacist-patient relationship. Third, the requirements are based on scientific evidence fully disclosed and evaluated by prescribers, pharmacists and others. Number four, there are scientific consensus that the requirements are necessary and represent the least restrictive means to achieve safe and effective patient care. Number five, the cost of the product and any associated products and services are identified for purposes of reimbursement. Mechanisms are provided to compensate providers for special services and duplicative costs are avoided. Number six, all requirements are stated in functional objective terms so that any provider who meets the criteria may participate in the care of the patient. And finally, the requirements do not interfere with the professional practice of the pharmacists, prescribers and

others.

ASHP recently conducted a survey of its members who have experience with restricted drug distribution systems to better understand the experiences of hospitals, pharmacists and their patients. Pharmacy department managers who responded to the survey generally supported the need for RDDS programs when necessary to protect patients from heightened risks associated with a particular drug. These programs do, however, present challenges in the hospital and health system setting, including problems related to timely access to drugs for patients and continuity of care.

Most respondents believe that RDDS programs can be improved and standardized. And that pharmacists' input into the development of RDDS programs would improve them. Sixty-eight percent of respondents believe that RDDS programs are necessary in some circumstances to protect patients. Seventy-five percent of respondents indicated that their hospital or health system is registered to

dispense products for one or more RDDS programs. Seventy-nine percent of respondents believe that practicing hospital and health system pharmacists' input into the development of RDDS programs would yield better programs.

Continuity of care was an important issue for many respondents when restricted drug distribution systems are used. Eighty-two percent of respondents indicated that continuity of care is compromised. Additionally 90 percent of respondents to the survey stated that RDDS programs compromised timely access to medication. In our outpatient pharmacy department, the most commonly dispensed RDDS medications are thalomid, Revlimid and clozaril.

In order to minimize burdens on the healthcare system, some standardization of RiskMAPs is needed. Additionally the programs must be transparent and ensure product availability in order to maintain provider and patient access to therapeutic choices. Restricting a particular product to dispensing by a specialty pharmacy

as an exclusive distributor may result in the unattended consequence of restricting the availability of the product overall.

ASHP also believes that distribution of medication through an exclusive distributorship should be avoided. The medication should come through normal wholesale pathways since compatibility with existing distribution systems will help to ensure access to medications and not disrupt the medication use process and potentially compromise patient safety. Additionally, while ASHP does believe that additional controls are needed when dispensing certain medications, minimizing the number of steps involved under a RiskMAP is necessary to reduce the burden on providers, patients, distributors and pharmacists. Furthermore, health systems already have in place processes to alert providers and pharmacists when a drug is considered high risk. For example, when an investigation on a new drug is provided.

A large number of medications dispensed from our

outpatient pharmacies at Johns Hopkins are high alert medications. High alert medications have a higher than normal potential to cause severe patient harm if dispensed in error. Dispensing rate for high alert medications in our outpatient pharmacies could be as high as four out of every 10 prescriptions dispensed. Many medications that fall under RDDS programs are high alert medications.

For patient safety purposes, special processes have been included in the medication dispensing practices for high alert medications, such as independent pharmacists, prescription verification, weight based dose justification for patient orders, and specific patient counseling practices.

Special steps identified for patient safety and the medication dispensing process are not always consistent with the steps included in the RiskMAP process. For example, the high alert medication thalomid, the pharmacist first must confirm the provider has enrolled the patient in the RiskMAP process, then must receive a

specific patient authorization number through the STEPS program to dispense the medication, and then ensure that the pharmacy is properly enrolled so that the drug can be procured for the patient.

These additional steps cause a prescription to be removed from our typical prescription production process. And the decrease in –- and this also decreases the time allotted to specific prescription dispensing processes that focus on patient safety. FDA should consider whether RiskMAP processes should be integrated into high alert systems already in place in hospitals.

Currently healthcare information technology does not play a large role in RiskMAPs. The use of technology varies among pharmacies, and even access to the web is highly variable. However, the availability of on-time, real-time enrollment via the computer for patients, pharmacists and others who may be required to register with a safety program would greatly assist quality prescribing, dispensing and patient use for those

pharmacies with computer and web access.

When determining whether and how to establish a restricted distribution system for a drug product, pharmaceutical manufacturers and the FDA should consult with practicing pharmacists to determine the most effective mechanism to preserve the pharmacist-patient relationship and continuity of care for the patient. And also ensure the requirements do not interfere with the professional practice of the pharmacists.

Pharmacists should be involved in the development of RiskMAPs and their evaluation in order to ensure the compatibility of the systems. However, the burden of data collection should not be borne by the pharmacists as this would constitute an undue burden. ASHP would like to work with FDA on the development of RiskMAPs and provide advice on how to standardize systems and develop criteria to determine which drug should go into a RiskMAP.

Over the past year, our outpatient pharmacy

began receiving prescription orders for the new anti-cancer medication, Revlimid. Only after a series of phone calls was our outpatient pharmacy able to procure and dispense this medication for our patients. A delay in the procurement of RiskMAP medications can cause a delay in patient therapy. It is imperative that outpatient pharmacy settings are able to receive these life-saving medications in a timely manner so that treatment is not delayed for our patients.

Research should be performed on the health system level with a focus on quality and access to develop a strong evidence base and healthcare system approaches, processes and tools that support appropriate use of medications with safety problems, or a reminder, and PLA RiskMAPs are being used or considered for use. Hospitals could perform the research in the post-approval process phase of the drug approval process and supply the results to FDA. Additionally, AHRQ could evaluate drugs with RiskMAPs and examine the outcomes. Frequent review

evaluation as to whether a drug must have a RiskMAP is necessary.

FDA should authorize research to determine how well existing and new restricted drug distribution systems are achieving their goals. Drug manufacturers and the FDA should partner with professional organizations in conducting this research. Various payers, such as the Department of Veterans Affairs, CMS, and others should be involved in evaluations of the effectiveness of RiskMAPs or pilot interventions, while pharmacists, physicians, patients and nurses are the primary stakeholders in health care who should be involved in the design and choice of risk minimization tools as well as providing feedback on their effectiveness.

The FDA Drug Safety and Risk Management Advisory Committee should craft recommendations to improve RDDS programs. The committee should analyze current FDA standards and recommend new policy in several key areas related to RDDS, including feasibility of standardizing

basic elements of all programs, ensuring timely access to drugs for patients, eliminating continuity of care problems, and lastly permitting exceptions from various RDDS program registration rules for those practitioners that meet pre-determined agency standards and requirements.

In the future, AHRQ and FDA should provide patient education, public awareness campaigns and on-going research to promote continued collaborations and contributions to the high quality, appropriate use of medications with RiskMAPs. Thank you for the opportunity to provide these comments.

MS. RYAN: Thank you for the opportunity to participate in the workshop today. I'm Mary Ryan, vice president of the pharmacy regulatory group of Medco Health Solutions. And I'm also chair of the Academy of Managed Care Pharmacies Legislative and Regulatory Action Committee. Today I'm speaking on behalf of the Academy of Managed Care Pharmacy.

AMCP is a national professional association of pharmacists and other healthcare practitioners who serve society by the application of sound medication managed principles and strategies to help improve healthcare for all. The Academy's 5,000 plus members developed and provided a diversified range of clinical, educational and business management services and strategies on behalf of the more than 200 million Americans covered by a managed care pharmacy benefit.

The Academy appreciates the opportunity to provide input to help in the development and implementation of mechanisms to minimize the risk associated with pharmaceuticals that have unusual safety requirements and which require ongoing patient monitoring. Managed care pharmacists are professionals who practice in managed care environments, such as health plans, pharmacy benefit management companies, and many government agencies, such as the Veterans Administration.

This is the group of pharmacy professionals

whose job it is to scientifically evaluate medications and design medication management plans, including such familiar (indiscernible) as formularies in order to effectively and efficiently serve the needs of their patient populations. Across the country, managed care pharmacists are managing thousands of prescription programs, including prescriptions filled in community pharmacies, integrated health system pharmacies, specialty pharmacies, ambulatory or outpatient clinics, and mail service pharmacies. The Academy's comments today will focus on the prescriptions dispensed by mail service pharmacies.

The Academy has chosen to focus on prescription dispensed in this specific setting because while mail service pharmacies dispense 18 percent of prescriptions in the United States today, this area of pharmacy distribution has not otherwise been represented on this panel. In addition, we will focus on the impact of RiskMAPs on prescriptions paid for by the health plans or

prescription benefit management companies or PPM's.

The Academy supports the concept of risk minimization plans when and as necessary to protect patients from the medication's risks. With increasingly complex medications in the pipeline, the need to use RiskMAP programs will become more common, and it is therefore important that RiskMAP programs are designed to be manageable for all concerned stakeholders, including patients, prescribers and dispensing pharmacies. We encourage the FDA to involve all areas of practice, including mail service pharmacies, and companies that manage pharmacy benefits in developing such programs.

Although it may appear to be more convenient for prescribers and pharmacists to have all RiskMAP programs function in a similar way, the Academy maintains that such a cookie-cutter approach would not best serve to protect patients from harm. In reviewing the RiskMAP programs for some of the medications requiring such programs today, such as isotretinoin, thalidomide and Tysabri, it quickly

becomes apparent that there are significant differences in programs based on differences in drug delivery and patient safety factors. The FDA will need flexibility to evaluate the goals and the use of individual RiskMAP programs and design programs accordingly. Ultimately the FDA may wish to establish a RiskMAP process separate from the drug approval process.

The Academy encourages the FDA to seek input from mail service pharmacy and from pharmacy benefit managers as it develops each RiskMAP program and provide information about developing programs as soon as such information is available. Although the FDA and the manufacturer may better understand the risks of newly approved medications at the time of approval, it is prescribers, pharmacists, pharmacy operators and pharmacy benefit managers that understand the potential impact on patients and practice.

RiskMAP programs limiting medication quantities may not allow patients to take full advantage of the

prescription drug benefit. For example, a RiskMAP program for a specific drug may limit the quantity of a medication allowed. The patient's benefit may require a co-payment as if a full 30-day or 90-day supply had been provided. The limitation may be necessary but should be introduced with an understanding of the potential financial impact it presents. In addition, pharmacy benefit managers must have information of RiskMAP programs as they make formulary decisions and decide upon internal safety protocols related to prior authorization requirements.

Pharmacy benefit managers all have experience with their own version of risk minimization action plans through safety-related prior authorization programs. Health plans and PVM's have (indiscernible) of their own prior authorization programs for medications such as erythroproetin, based on published literature before the FDA released public warnings about such products.

Upwards of 90 percent of Americans receive the advantage of some type of managed pharmacy benefit which

provides such initial risk minimizations safeguards. The FDA should take advantage of the opportunities to implement safety restrictions that can be implemented through pharmacy benefit managers, mail service pharmacies and specialty pharmacies. Rather than restricting the initial distribution channel for a medication by using only one wholesaler which can be problematic for pharmacies nationwide and drive up costs for patients and providers alike, RiskMAP programs can be structured to take advantage of the specialty skills and systems for patient monitoring represented by pharmacy benefit managers and some pharmacies.

Additionally, the Academy would like to ensure that the FDA is aware of state legislation and regulations that may intersect with some RiskMAP programs that restrict distribution to certain pharmacies. Although such programs may work for most patients with a commercial pharmacy benefit, some state programs, for example Medicade or some state employees benefits, may carry an

additional barrier by requiring that prescriptions be dispensed by pharmacies within their state. And several Medicaid agencies do not allow mail order pharmacies services creating challenges that may prevent patients from receiving need of medications.

The FDA must include stakeholders that are aware of such restrictions when RiskMAP programs are being developed. The Academy understand that when developing RiskMAP programs, the FDA is motivated by the best of intentions when it comes to patient safety. However, the complexities and logistics of today's pharmacy benefits and pharmacy distribution systems must be taken into account. All stakeholders must be involved early in the process.

Additionally, as the FDA continues to approve additional RiskMAP programs, it is imperative that these programs are structured to include an ongoing evaluation process with representation from the range of healthcare provider groups to continually analyze whether such

programs either are or could impede access to necessary medications.

The Academy recognizes that the FDA may not have had the resources and stakeholders to present this perspective in the past. However, AMCP's members represent payers and pharmacy providers both of which are available to provide a value of resource of information in the future. Thank you.

MS. DUCCA: Good afternoon. I want to thank you for the opportunity to be here and give you the HDMA perspective on RiskMAPs. I also want to thank Ilisa and Sandy for their kind comments about wholesale distributors and how important we are in this whole system because that helps to frame up the talk that I'm going to give today.

I'm going to give a brief overview of the wholesale distribution industry. I assume that many of you in the audience are not familiar with what we do. And that in order to be able to understand our comments and recommendations, it's important to have a little bit of a

baseline understanding of the industry as a whole.

I'll briefly touch on who regulates wholesale distribution. I will use iPLEDGE as a case example that's the basis of the comments that we're going to be giving today. So I'm going to be talking really just about the restricted distribution approach to RiskMAPs. We've already commented on the med guides program a week ago. And so I'll just talk about the restricted distribution programs for today. And then I'm going to give you some general observations about RiskMAPs and then some specific recommendations to follow as we move along in this area.

Okay. First of all, the Healthcare Distribution Management Association is a trade association with 40 primary full service healthcare distributors. We call them healthcare distributors because although drugs are the basis and the most predominant product that they distribute, we also distribute medical devices, health and beauty aids, and other things. Anything that you might find in your local pharmacy has found its way into the

wholesale distributors warehouses.

There are distributors who are national in scope, some are regional, meaning they'll concentrate on just distributing in one part of the country, and some are specialty, meaning that they may focus in on a certain type of product or a product that requires special handling, if it needs special refrigeration, for example, or freezing or that kind of thing. And so there are distributors that just focus in on certain specific elements of the prescription drug market. There are among HDMA's members 151 distribution centers that service 50 states and territories. And by distribution center, I mean a very large warehouse.

Now I'm going to give you some more statistics just again to explain who we are. First of all, this is just kind of a roadmap for how the distribution system works. It's extremely simplified. I'm going to step away. I hope you can hear me as I step away from the podium. But what the wholesale distributor does is to

purchase products from the manufacturers, and usually prescription drug products, but also over-the-counter products, some medical devices and EDA's. They will buy these up and store them in their distribution centers. And then they sell them to all of the pharmacy sites that you see here. And they may be clinics, chain drug stores, independent drug stores, mail order physician offices. So the organizations that you see that purchase the products from the wholesale distributor can do their homework in a one-stop shopping mode. So instead of having contracts with hundreds of product manufacturers, literally each of these dispensing sites can go to one location for all of their needs.

Just to give you a little bit more data here, an individual wholesale distributor stocks about 24,000 stock-keeping units. That's individual types of products, maybe the same product packaged a little differently or larger number –- and an amount in one product, but we call them stock-keeping units. And typically they have more

than 500 suppliers. They ship to –- overnight they ship about 60,000 products. This is one wholesale distribution center per night, 60,000 products. They deliver products usually overnight and sometimes the same day. And they typically have over 700, you know, in the 760 range number of facility sites that they ship to.

And this is a picture of a wholesale distribution center. What this is the receiving site. When the manufacturer ships products into the wholesale distributor's warehouse, this is a picture of one of those sites where they're actually received off of the truck. Now I'm just going to comment that you're going to see these pictures. There's no people in them. There are various reasons for that, including security of the individuals that might be working in these facilities.

This is the picture of the storage site. This is a manual picking area. You see lots of products there on the right on these stacks and stacks and stacks of shelves. Let me tell you that this is just a small area.

The warehouse itself is many, many times this size, but this is just one perspective of what happens there.

You can see in the bottom left there the conveyor belts. Overnight there will be hundreds of totes that are put in these conveyor belts. And as the people working there pick the products off of the shelves, they'll put them in these totes and the conveyor belt will take them out around to the outgoing area.

This is a picture of –- if you look at the left here, this is what they call an A frame. It's an automatic dispensing piece of equipment. You can see the drugs that are stacked up there on the left in this facility. This is tied into a computer. You can automate the ordering process and have these products just dispensed to this computer picking system. They drop down and they get picked up and move along another smaller type of conveyor belt.

And this is an outgoing, shipping out area. You can see a few of these blue totes there. They look like

the Montgomery County recycling bins to me. But they're on the left side. But this is –- you know, the conveyor belts will come down these belts and they'll get loaded on and moved from here onto the trucks as they move out of the warehouse.

Just a few more points that I wanted to bring to your attention is that nearly 80 percent of the prescription drugs handled in the United States are handled through distributors. So even though you go to your pharmacy on the corner or whoever, they have probably been housed at a distribution center before you picked them up from your pharmacy.

We are very happy about the fact that we can save the healthcare system by an estimated $10.5 billion a year that's due to the efficiencies of ordering of storage and pharmacies that have the overnight immediate shipments to them. They don't have to carry a lot of storage area, and we can realize a lot of efficiencies by having this distribution system in the U.S. We do this all with an

extremely thin, razor thin profit margin of 0.78 percent per product. So as you can see, it's a lot for a little.

We are heavily regulated. The Food and Drug Administration does regulate the wholesale distribution programs in the country. They regulate us under the Prescription Drug Marketing Act. And they set minimum standards that we must follow. The DEA, the Drug Enforcement Administration, also regulates controlled substances and what they call List 1 chemical precursors. So for controlled substances, narcotics, whatever, there are special regulations on handling and safeguarding those drugs.

And the states are actually the primary licensor entity for wholesale distributors, although FDA sets the minimum standards, the states can set –- they actually issue the licenses. They usually have complicated and are getting more complicated license application procedures. They can be more stringent and they are going in a more stringent direction than FDA is. We've seen that in the

last few years. And they conduct inspections.

Let me talk a little bit about iPLEDGE and kind of explain this program from our perspective. And I want to –- like I say, I'll use this as a case example to explain why we're recommending what we're recommending.

iPLEDGE was the program whereby four manufacturers of isotretinoin products got together, and under the umbrella of Covance, Inc., which is a firm that is administering the program for all four manufacturers, they set up the program and there are –- you know, everybody knows that there are special requirements for the prescribers, for the patients, for the pharmacies. But there are also special requirements for the distributors.

And so we heard about the program actually only a few months before it was scheduled to start up. And we got involved right away as soon as we found out that it was going to be impacting our members as much as it has. We formed a task force internally to start talking about

the program. HDMA needed to make our members aware of it, and our members needed to make their questions and concerns. They need to present them to us so that we could help them out. And we also started working on inputting into the requirements. We are to this day still working with FDA, Covance, and all the other stakeholders that are involved in this program.

What are the requirements of iPLEDGEledge for the distributors? Well, first of all, a distributor who wanted to be in the program had to register. And they had to agree to restrict the distribution of isotretinoin products according to the program outline. And that meant they could not ship isotretinoin to any pharmacy that was not registered and activated in the program. And they had to agree to supply certain required data regarding the distribution of their products. Sounds very simple and very straightforward. However, as we began to delve into it for a wholesale distributor, this is not as straightforward as it looks just on the surface.

Many of the discussions that we had with FDA and with the stakeholders were talking –- were starting just at the point of how do we know whether or not we can meet the requirements? Many of the requirements were still pending. So the first step was to –- for a wholesaler was to decide whether or not they were even going to register in the program. And yet they had to make those decisions while the elements of the program were still in development, at least the elements they were going to have to meet. That's a tough decision when you're talking about the razor thin margins that we have. You don't even know when you're going to be able to meet the program's requirements.

One of the key operational requirements was going to be setting up a system to match your customer list with the activated pharmacies that were also in the program and permitted to dispense the product. And again if you consider that you are trying to match over 700 sites with literally tens of thousands of pharmacy sites

that were going to be part of the problem –- not a part of the problem –- part of the program –- what a slip that was –- if you consider what it would be like –- you'll remember this talk. That's for sure –- if you consider what it would be like to try to do that in what was initially envisioned as a manual comparison process, originally we were going to receive a text file and have to manually do the comparisons. We had a few of our members in something of a state of shock to think what it would be like to try to do that.

So we had to have many discussions about how to convert these lists into an electronic format that was going to be compatible with the various wholesale distributors and their formats. Now again you have four manufacturers essentially manufacturing the same product. But for HDMA, you have 40 distributors, again with 24,000 SKU's that they're managing, and so getting something that is easy to use and doesn't disrupt the rest of your distribution system was going to be a challenge that we

had to work out. So we came up with, you know, some ways that that could be sent out to the wholesale distributors that was not a manual match.

Some of the other questions and issues we had to work out was how often would we do the matching. What if the –- Covance was going to send us a list every day and update their website every day. Well, what if you get the update and the products are in the totes and on the trucks and heading out to the pharmacy and you get an update and find out that that particular pharmacy is no longer activated for whatever reason. They've decided to drop out or something else happens. Okay. So where do you draw the line? So we had to work out some of those things. We had to work out when are we going to receive these lists so that they could be matched by the computer.

We also had begun talking about the data that were going to be reported. There were a number of different kinds of data that were supposed to be part of the program. A couple of the different kinds of reporting

we decided were not necessary, given the way the ordering system works, and so –- but that had to be talked through with FDA and with the sponsors of that –- so there was a common understanding. Some of the data didn't even exist. They were just some assumptions there. So we worked all that out.

But the data that is still going to be reported, there are still some –- it's compliance data. There's an idea that we should be supplying data regarding how many products might be shipped to what pharmacies so they can check and make sure no one is over-ordering, or no one who is not registered is ordering and that kind of thing. So that part of the reporting is still under development. So there's still some efforts that we're going to have to make in the future to work that out.

To talk about operational implementation, what did we do to get all of this in place? Well, the various distributors did so, and, you know, each has a different system. And so they did so in their own way, but most of

them had to create new software to do the matching. So they compared their customer list to the lists that are now coming out of Covance every day. They performed –- this matching initially was quite a feat because again you have literally tens of thousands coming in a single e-mail essentially from Covance. And we only had about seven business days in order to get the programs, the software up and running. We had seven business days between the first receipt and the start of the –- the drop-dead date for starting the program.

We also had to set up and revise some of our ordering software. Most of the product ordering from pharmacies is done electronically. So our members had to make sure that in those electronic systems, a pharmacy that was not activated was not allowed to be ordering this particular product through the computer. They wanted a flag, they wanted a reject system. They wanted some way to notify the person receiving the orders that this person should not be ordering the product.

We had to do a certain amount of training of internal staff. Customer service representatives had to be trained on what the program was to be able to answer questions from our customers. You know, I'm an activated pharmacy. Why aren't I on your list. Or I didn't even know there was such a program. What do I do to sign up. We had a lot of that initially. So they had to be trained.

We also do as you can imagine a certain amount of training and counseling of our customers. Many of the pharmacies that are now activated pharmacies didn't even know about the program until the day they got the flag that said you can't order this product anymore. So that was –- initially it was –- one of our challenges was to work with them to make sure there was an understanding and to get them directed into signing up for the program.

On occasion, there are some special shipping arrangements that we might go through. This tends to be a circumstance where the –- as you know in iPLEDGE, there's

a short window of time between when the patient takes the pregnancy test and when they can get the product –- fill the prescription. So at least initially, not so much now, but initially some of our distributors made special shipping arrangements, you know, in order to get the product out there in time.

And some are looking at –- right now they're looking at implementing EDI systems. EDI stands for electronic data interchange. It's a warehouse tracking system, if you will. It's used by the wholesale drug industry. I believe that it is used by other industries or something similar, for example, food distribution I think uses something similar. But you would track the amount of products you have in inventory and you report that information to the manufacturers so that helps them plan their production schedules, things like that. How much you have in inventory, how much is sold, where it's being shipped to, all those kinds of things. So in order to get ready for the reporting that we anticipate will be

required down the road, some of our members have this, many do not. And so they're considering whether or not they're going to get involved in EDI.

We still have some things that need to be determined as I mentioned earlier. I won't belabor this. But the product flow data, the data that FDA and the sponsors want to review in order to make sure that the right amounts of products are going to the right places, we still need to be discussing who's going to receive the data, how frequently, what is the format that's going to be required. And that alone is going to be a challenge for everyone because even though some of our distributors use EDI, it is not as standard as what Covance and the others and sponsors are going to need in order to do their evaluations. And since many don't use EDI, there's another hurdle that has to be overtaken and dealt with. So if the format has to be one in the same, we're going to be running into some additional challenges.

We also have asked for some clarification. Once

they get the data, what is it going to mean to be out of compliance? Is one shipment? Does that mean you're out of compliance? Ten, 20? You know, what does it mean and what are the consequences?

And we are still looking for some simplifications in the program. We've had some conversations with Covance. I think everybody's in agreement that, you know, these are all good things to do. I think the program is so big, though, that it's very hard to do it all at once or in a –- even, you know, in a period of months, it's very hard to pull it all together and make sure it's all working in there. Just some other priorities that have had to come ahead of some of the ones that we've been discussing.

Just want to talk a little bit about the big picture on restricted programs, restricted distribution programs. And I think this is important because there needs to be a realization that getting the product to the patient is also important, as well as having a safe

product with the patient. If the patient doesn't get the product at all, you've still got a problem.

So starting with what wholesalers and wholesale distributors are going to be able to be part of the program, they did make their decisions to join based in part upon how clear the requirements for the program were for them. Initially there is, and there still is very little in writing about what the program requirements are and what you have to do to comply. But I had many phone calls from our members saying, well, you know, when are they going to send us the files, what are they going to look like. And I couldn't answer those questions, and they were trying to make their decisions on that. So being clear about the program is going to make a difference in whether or not wholesale distributors are going to be able to participate.

Another point I really want to emphasize is that I know we're talking about risk on a drug by drug and patient by patient case. But if you consider the

wholesale distribution system, what you do for one drug potentially can impact all the drugs in the system. There are, for example, existing business arrangements that the wholesale distributors have with their suppliers or with their customers. Perhaps the business arrangement is to buy a certain number of drugs at a certain price. And when a RiskMAP comes along that changes that dynamic –- maybe there's going to be fewer drugs available, or maybe there's going to be –- it's going to be a lot more expensive to handle and manage that drug, it does have an impact.

How you choose whether or not a wholesale distributor can be part of the program is going to directly impact their ability to remain in business. One of the big benefits of going through a wholesale distributor for a pharmacy is the one-stop shopping idea mentioned earlier. So if that one stop doesn't have a drug that you want, or a key drug that you want, and you have to go elsewhere, you may be taking all of your

business elsewhere. And that can significantly affect the wholesale distributor. So if they have trouble remaining in business because only a few products can only be obtained from a few other distributors, they have a serious competitive and viability issue.

It also –- it clearly affects non-RiskMAP drugs. This may not be immediately obvious, but if we have many more drugs coming into the system in a similar type of restricted distribution program, we are going to have trouble with maintaining those computer ordering systems and creating the cutoffs and the flags and so forth. And this is not just for our smaller distributors. I've heard this from our larger distributors. The system can handle only so many drugs, but there's only so much computer capacity they have before it will start to slow down that ordering system. And yes, other drugs would be potentially affected.

Another point, and some of the other speakers have talked about the costs and reimbursement. That is

also going to be key. The programmers who rewrite the ordering software and so forth, they need to get paid, you know. And that additional funding has to come from somewhere. So we're going to have to think about how we're going to handle the reimbursement for these products.

How compliance is evaluated is also significant. I talked about the data reporting for compliance. That's –- how that is structured and what you do to define being in compliance and how you provide that information, that will have a very significant impact on such a program and its viability.

Another factor to consider as you're moving on RiskMAP programs is what will this do to Internet drug purchases. If it is very difficult for an individual to get a drug product, or they have to wait seven days and then the pharmacy doesn't have it, or whatever, it might be very easy to just turn to the Internet and order it on-line.

We would like to recommend getting to know the wholesale distribution industry better and what impact that will have. And we also want to comment on the feasibility of future programs because like I say, if the more you pile on, the more requirements, the more difficult it's going to be for your wholesale distributor to maintain their programs.

Just a few specific recommendations for future programs, I can't say it enough to prepare, prepare, prepare before you go live. Involve us as early as possible. We'll come in and talk with you. We will work through these issues. We also strongly recommend testing before you set up the program. One of the best things that we could do would be to test those ordering and matching systems ahead of time, make sure there's no glitches or problems. We did find problems in pharmacy numbers and other things in the iPledge program.

We urge defining these requirements in writing, being very clear, thorough. That helps us out in making

decisions, not just to participate, but where we want to go with it.

Standardized. We've heard that term before. If it's feasible to standardize for wholesale distributors, that would be helpful as well because the more differences you have among the programs, the more difficult it is to be involved with them.

We also urge being aware that there are other regulations that affect wholesale distributors. Let's not be in conflict with those. I'll mention the PDMA in particular because that has gone into effect as of last December. And so we just want to make sure that if there is a requirement for wholesale distributor, there are no conflicts with other requirements that may exist elsewhere so that you are sure that your distributor can be part of the program.

And then finally we just advise that this is -- it's very complex. It is costly. It affects a lot of people. And we urge that you use a restricted

distribution program only if there really is no other way and only in extreme cases and extreme risk cases. And that ends what I was going to say. Thank you.

MS. BERNSTEIN: Thank you to all the speakers. And before we go to any questions here, why don't we open it to the floor. And the format we're going to use is you'll ask a question, and then we'll answer it one at a time. I'm about as coordinated as Mark was to try and organize all the questions at once. So are there any questions from the floor? Yes.

MS. KARWOSKI: Claudia Karwoski with FDA. We've noticed that a lot of the programs are now coming in, and they're proposing these specialty distributors. And just from an implementation perspective, it sounds like sort of an easier way to go. So I wonder if you all could just elaborate a little bit on what some of the disadvantages would be using the specialty distributors versus retail pharmacies.

MS. RYAN: I think there are probably a lot of

advantages to using specialty, depending on what type of drug you have. However, from a pure plan perspective, when you have only one distributor, you have absolutely no ability to negotiate the price, etcetera. So the reimbursement becomes somewhat of an issue. So from a pharmacy benefit management point of view, I would say that's probably the biggest issue. There are times, however, when it makes absolute sense to use specialty pharmacies –- I was saying that the disadvantage from a pharmacy benefit point of view is that you don't have an ability to negotiate price because you have only one supplier of the product.

From a –- there are also, however, advantages to using specialty pharmacies because there are certain types of products that it just doesn't make sense to send into wide distribution. If you have a product that only has about 100 patients or so in the entire United States, it probably isn't economically feasible for a manufacturer to try and make that readily available to 55,000 pharmacies

or a plethora of wholesalers. I mean it just doesn't economically fit. So there's lots of reasons to use specialty pharmacies and also some reasons not to.

MR. THOMPSON: Also from an operational perspective, standardization seems to be the reoccurring thing that we're all talking about. When one of our outpatient pharmacies orders a medication, we use an inventory automatic perpetual system where (indiscernible) order points are based off of historical usage, so we can meet our patients' needs. It's an on-line adjudication to our distributor where we receive the drugs back. It's a five minute process.

For some of these RiskMAP drugs, it becomes a call to the distributor by one of our pharmacists, by one of somebody assisting one of our pharmacists that could take 10 to 15 minutes to order the drug because you're speaking to a live person. When you add more and more drug to the system, it doesn't sound like a lot, but that adds up to a great deal when you're caring for 2- to 300

patients in a setting in a single day.

MS. DUCCA: It wasn't quite clear to me whether you were talking about specialty dispensing or specialty distributing. But let me just address it if you are talking about specialty distributing.

You really need to be careful that those specialty distributors can reach the areas of the country that you want the product to go to. That varies from area to area of the country, and distributor to distributor, so you need to be careful who you're selecting can actually, you know, has contracts and existing arrangements with the hospitals or other settings where the drug is going to be dispensed.

And again, as I mentioned in my talk, there's a real question about the viability of distributors that are not selected for being part of, you know, whatever program it is. You didn't say specifically any of the drugs or whatever, and so we'd have to look at it on a case by case basis. But if you are going to carefully lay out your

program, it may be okay, but just be aware that it may end up being a real problem for that distributor to remain in existence, depending on how it's set up.

MS. BOUGH: Similar to some of the previous comments, I think there'd have to be great care taken with the development of a risk management program that was limited to a specific distribution system to make sure that pharmacists knew where they could order that product and not trying to do a blanket call to a wholesaler and then finding out that, you know, they're not supplying it, but an educational campaign so that everyone is aware if it is restricted to a specific distribute site, that they know how to contact them and what specific procedures it takes to actually order that product.

MR. GREGORY: Just one more comment from the community pharmacy perspective, you know, we evaluate programs and placing medications in pharmacies, you know. Two things. One, the complexity of the program, two, there is a cost factor also with stocking all your

pharmacies with a particular medication. So not to say there can be a limited distribution program with setting up, you know, a certain amount of pharmacies to cover a network of needs. So it doesn't have to be 55,000 pharmacies, but it would be based on geography and need.

MS. BERNSTEIN: Several of you, all but one of you, suggested that greater standardization is needed. I was wondering if you want to go into any further detail in terms of specifically in what areas and how could that be done.

MR. THOMPSON: Sure. From a prescription dispensing process working with third party payers, everything's done in real time through an adjudication process. The bill is dropped. Our screening is done electronically through computers. It's a real time process.

For a lot of the verification processes with a lot of the various RiskMAP programs, it becomes a phone call to a screening station to verify the authorization

number. It becomes a screening stop to make sure that you can procure the drug. And this really takes the entire prescription and the entire patient care out of our prescription process.

When you're dispensing a large number of high alert drugs during the day in order to make sure that you can care for each patient, talk to each patient, give them the care you need, you want to put that entire process into one system so that you're not breaking those different pieces out.

MS. BERNSTEIN: Anyone else want to comment on that?

MR. GREGORY: I would say –- I mean there's a great opportunity to standardize just the training, education and communication process because there's different ways of reaching out to the pharmacy industry, and if we could make, you know, a common platform for training and education, that would be a great step.

MS. BERNSTEIN: And on that point, where would

that training and education come from? The manufacturer, from pharmacy –- or from FDA, from some other place? Where would you envision that?

MR. GREGORY: Well, the education comes down through the pharmacy industry, so, you know, programs similar to this, like HIPAA or Medicare Part D; we use some common learning management systems to final training programs down through our industry.

MS. BERNSTEIN: Anyone else?

MS. BOUGH: I think with the different tools that are out there right now for the risk management programs, what we've heard from pharmacists are that with all the different options, they just want to know what's going to happen with each program, especially if there's new programs coming up that they haven't had to try to figure out by now.

When pharmacists are in a setting that may not dispense some of these medications on a regular basis, or if they have floater pharmacists coming in to a particular

pharmacy, there's just unaware of all of the details that go into some of the programs. So some standardization –- if there's a risk management program with a certain level of risk associated with that product where –- and that may vary to a higher risk level, depending on the product, but those different programs have some standard procedures and processes that go with them so that it's not varying across manufacturer's and that there's a standardization of what the program's going to look like at a baseline so that the pharmacists and prescribers and patients are really aware of the general concepts that would be part of those programs. And that also relays into education and what we can do to get the word out for what these programs really are.

MS. BERNSTEIN: Any more comments on this point before we take a question over there? Oh, okay.

DR. KWEDER: Sandy Kweder, FDA. I guess I want to press that a little bit because one of the things that we faced is a lot of –- every one of these programs is –-

most of them are there for one reason or another. They're different. I want you to –- if you could maybe give an example when you're –- I don't know what you mean by certain elements being standardized. I guess I just don't really know what that –- other than that you're always calling –- I'm just envisioning while –- if there was some central program where you always called the RiskMAP hotline, and that's how you did your checking. But I don't think that's what –- I don't think that's all of what you mean. So if you could maybe make up an example, or give a real example, it would be very helpful.

MS. BOUGH: As an example of some standardization would just be something as simple as when is a lab value of whatever the therapeutic indication is for the product. If a lab value is required, is it going to be before the dispensing or is it 30 days after? Something as simple as that type of standardization so that the people involved with prescribing and then dispensing the product and having that interaction with

the patient aren't put into a position where they're in a confrontational setting with the patient because they can't get them the medication because they don't have a lab value. Whereas the program that they just worked through with the previous patient, maybe the lab value came in prior to the prescription, something along those lines.

MS. KWEDER: So is it more standardizing some of the communication about the program so that it's implemented the same way? Is that what you're getting it?

MR. THOMPSON: I think it's the whole process. Take a hypothetical drug, for example. Prescriptions presented to the pharmacy. If there could be one standardized place for a pharmacist to go to know that this is a RiskMAP drug, these are the steps we need to do to receive this drug, and we will be able to receive these drugs once we meet the steps.

Often for example if a drug comes to one of our pharmacies for the first time, and I think Mark or

somebody stated earlier, we don't know that the steps we have to take till we try to procure the drug. Take it a step farther once you go through those screening tools and you're able to procure the drug, each drug is going to have specific patient consultations, specific tests that can't be standardized. There's going to be different procedures for each drug. But to verify that you took those steps, to verify that that has taken place in a more real time format is really I think the preference.

And then take it that next step, and I think we heard this earlier today also, from a record-keeping perspective, if there's a way to keep these records electronically –-

MS. RYAN: I think this is a place where actually managed care plans could help. We do send messaging with every prescription, and if we had –- if the issue is that the pharmacist doesn't understand which drugs need these sorts of programs, we could certainly send messaging on those drugs to the pharmacies that this

is a certain type of drug, and it has to go through a RiskMAP program.

I could tell you right now then when the FDA withdraws drugs from the market, we send and stop prescriptions coming through the claims system to alert pharmacies that they should not be dispensing this product. We could do similar sorts of things working with the FDA or whoever the right entity is to send messages on a real time basis to pharmacies and pharmacists before they dispense these products, so if they understand these are those special products that require some special handling.

MR. GREGORY: One parallel that we might talk about is within the Medicare Part D program, there was one good thing that came out of (indiscernible), the technology solution and the (indiscernible) where CMS actually went out and contracted with a company that gathers all of the information to a Medicare Part D beneficiaries. Pharmacies can actually send a claim to

the pharmacy dispensing platform to check eligibility for Medicare Part D beneficiaries to find out what plan they're on and where they're at with their in their benefit and things like that. So that's just an idea of something that can sit from a technology perspective amongst, you know, the nice communication network that pharmacy has to help facilitate the standardizing process.

MS. DUCCA: I'll just give a quick response. We, for the wholesale distributors are mostly talking about operational standardization, one of our concerns, for example, is that once the data reporting system is set up, that we may be required to send data to four different manufacturers of isotretinoin products. And we only want to send the data to one location that is incrementally more expensive to set it up to go multiple locations. So that's the type of thing we're talking about in standardization.

MS. BERNSTEIN: Question?

MR. KAHN: Sidney Kahn, Pharmaco-Vigilance and

Risk Management, Inc. I have absolutely no knowledge whatever of the retail or house-held distribution systems, except as a consumer myself at my local pharmacy. But it strikes me that there's supposedly something like 5,000 products on the U.S. market today. And we've seen that there are RiskMAPs in place at the moment to something like 30. And most of those tend to be for very, very limited indications and populations.

So it would seem to me that the average pharmacist to average distributor is quite likely never to encounter one of these, or to encounter one very, very rarely. So from the perspective of (a), the burden of an individual distribution chain, it wouldn't seem to me –- and again, this might be my ignorance of the system speaking –- that this would pose such a tremendous burden, although I do appreciate, and I think everybody else would, the fact that once you have to step outside to a normal process, it creates additional complexity. But what kind of burden are we actually talking about simply

based on the statistics we have at the moment? Thirty odd RiskMAPs out of 5,000 products at a total patient exposure for those products as I have no idea what, but probably not too many.

MS. BERNSTEIN: Anyone want to address that?

MR. THOMPSON: I think it really depends on the practice setting of your pharmacy also. For example, on our different campuses, we have oncology specialty pharmacies. We have pharmacies that work with patients living with HIV. And those settings, just the patients that are coming down, they're coming from their prescriber. The types of prescriptions that they're bringing, it's I guess a more focused area where you're going to see more of those 30 drugs come to the pharmacy much more frequently than, say, the other 4,700.

MS. BERNSTEIN: And actually just another comment on that. We heard at the medication guide meeting that medication guides are one type of tool used in RiskMAPs that there are a lot more than 30 drugs. I don't

remember what the actual numbers were, but with generics and classes of drugs using med guides, the burden, at least what we heard, was significant.

MS. DUCCA: The wholesale distribution industry is extremely competitive. And if –- it's not just who gets selected to become a wholesale distributor in a restricted distribution system. It's who's left out. If you are left out of that system, and your customers who need that drug go to your competitor for that drug, they may start going to that competitor for all their drugs. And so it has a real significant business impact.

And I think 30 is probably a minimum number to begin seeing that impact. But I think if we start adding more on, we're going to be –- I could tell you our members are going to be pretty concerned about their ability to remain in business and to remain competitive because the convenience for a pharmacy to just be able to go to one place for all their drugs, not just this one special drug, for them that may outweigh their decision to stay with a

distributor they've been doing business with for years.

And sometimes the decisions about whether or not a manufacturer will sell to a specific distributor is solely based on convenience. It's not based on, you know, safety or, you know, any of those things. It's just based on business convenience. And so there's a real concern that the ability to stay competitive may be impacted by these programs.

MS. BERNSTEIN: I think our last question, looking at the time at least on this clock –-

MR. FILLER: I'll make it really quick. I don't want to keep everybody. Darren Filler from I-Pro. I just want to clarify something that I think Mr. Thompson mentioned earlier at your pharmacy, that four of 10 prescriptions might meet this criteria, or you classified them as high alert.

MR. THOMPSON: Yes. Four at one of our outpatient pharmacy settings, four out of every 10 prescriptions we dispense are high alert. High alert

encompasses much more than just risk medications, the anti-coagulants, anti-cancer medications, narcotic pain medications. But a lot of RiskMAP drugs fall into this high alert category where we have many different safety checks in place for the patient.

MR. FILLER: All right, thank you. And going along that point, and I think expanding on what I believe Sidney here was getting at earlier, there are many drugs, and you just admitted yourself, that are high risk drugs that are outside this list. And my guess is that there are far more patients exposed to those. And that what we're discussing here is a system, and I can understand that coming from the drug development and marketing perspective and the FDA perspective of getting drugs available to the public, why it makes sense to try and develop systems to accommodate them.

But from a holistic, public health perspective and from understanding and listening to the mission statements of the various pharmacy organizations, if

public health and all those things are part of your mission statements, might there be other drugs that you would also want lab data, diagnoses, things that would actually help you, you know, pursue your mission?

And I guess to make it more articulate, are there specific parts of the RiskMAPs that you could do away with that are prohibitive to you? Whereas are there other parts that are actually beneficial to you and your mission to proving patient care, especially in light of Part D, the development of potentially integrated data sources, quality assessment tools at pharmacy and plan levels?

So specifically are there parts of the RiskMAPs that are so egregious or that really need to be systematized that they're obtrusive? Are there parts of the system for select drugs that actually are helpful to patient care that could go beyond that list of drugs?

MR. THOMPSON: My response to that would be let's –- the response I think from the statements also –-

let’s take these RiskMAP drugs and try to find a way to put them into the processes that we have for high alert to make it a standardized process for safety of all patients receiving high alert medications.

MS. BERNSTEIN: Well, thank you all. Thank you to the panelists for taking the time to come here, and for your really good suggestions that we’ll take back to the FDA. Thank you.

MS. TRONTELL: Thank you, Lisa. And to thank you all. It’s been a long day. We’ll actually start tomorrow’s session with a recap of today’s activities.

When you depart this evening, please take the red tag you were issued, use it to exit, and return it. Tomorrow morning if you’re bringing luggage, it could potentially delay it. So again I thank all of you who came early today. If you can do it again tomorrow, we’ll be able to start on time. Thank you.

(Off the record - 4:45 p.m.)