THE BROOKINGS INSTITUTION

ENGELBERG CENTER FOR HEALTH CARE REFORM

FORUM ON POST-MARKET EVIDENCE

Friday, June 13, 2008

9:00 a.m. - 12:30 p.m.

Washington, D.C.

ANDERSON COURT REPORTING
706 Duke Street, Suite 100
Alexandria, VA 22314
Phone (703) 519-7180 Fax (703) 519-7190

C O N T E N T S

C O N T E N T S (Cont.)

Key Challenges and Possible Solutions:

* * * * *

P R O C E E D I N G S

MR. MCCLELLAN: Since you all got quiet so quickly, I'm going to go ahead and start in less than 2 minutes. That was very impressive. I'd like to welcome you here to this forum on Post-Market Evidence sponsored by the Engelberg Center for Health Care Reform at the Brookings Institution.

I'm Mark McClellan. I'm the director of the center and we're very pleased not only that so many people who know so much and care so much about the safe and effective use of drugs are here, but that you made it through any number of obstacles. I understand there are power outages and traffic blockages this morning and it's nice to see everyone here despite that. I think that's an indication in fact that we are talking about a very timely issue today. The last few years have been marked by heightened public concern about the safety of drugs that are on the market with some high-profile instances of strong new warnings being added or even withdrawals of drugs that had been on the market for some years and used by

millions of Americans. Steps to learn more effectively about the safety and effectiveness of drugs and actual use has become a top public health concern.

As you know, last year Congress enacted the FDA Amendments Act which include some major provisions related to the monitoring and use of drugs after they are on the market. On top of that, FDA has been taking many new steps to enhance its surveillance-related activities. This conference focuses on some of the most important provisions and issues related to these very important topics, and in particular, building on pilot programs and expanding capabilities of our increasingly electronic health care system, Congress called for the establishment of an active surveillance system for drugs and other medical products. This will be established on an aggressive timeframe according to the Congress. The systems of databases for active surveillance is expected to reflect the experience of 25 million Americans by 2010, just a couple of years from now, and at least

100 million Americans by 2012. In addition, the law requires the FDA to seek expert input on a full range of issues related to using this kind of surveillance system including risk identification and risk assessment, risk communication, as well as risk management steps and risk mitigation steps.

With these new authorities, with new funding and with improving electronic data and statistical methods and with new opportunities for broad-based support for these steps, there is considerable momentum for working together to establish a fundamentally better system for post-market evidence on drugs and other medical products. With the new law and the new opportunities, we may be entering a new era in terms of how drugs are evaluated and how they are used once they are on the market.

We're very pleased today to bring together such a diverse and talented set of individuals to address these issues. Representatives from the FDA and from other government agencies, from the academic community, from consumer and patient advocacy

organizations, from product developers, from health plans, and from the provider community all join us today, and that's good because there's a lot of work to be done.

We'll address a range of issues related to these opportunities for better post-market evidence. We're going to try to do that in the form of a structured discussion with the goal of getting a lot of ideas and issues on the table and providing some opportunities for comments as well both today and in follow-up to today's session. These perspectives will be coming from a broad range of experts. First we'll hear from the FDA. The Commissioner of Food and Drugs, Andy von Eschenbach and as well Deputy Commissioner Janet Woodcock, will discuss the FDA's recently announced Sentinel Initiative and a number of other issues related to the agency's vision for improving drug post-market surveillance as part of implementing the new law and responding to these new opportunities.

Then we'll expand on many of the issues in that discussion with a presentation from Marcus Wilson, Rich Platt, and Janet Marchibroda. They're going to talk about a potential framework for implementing active surveillance using a distributed data network and about some of the building blocks for this network, building blocks that already exist and in many cases are already being used to develop better evidence on the safety and effectiveness of medical products. As you'll hear, they're working together as part of a broad-based effort also in collaboration with Ingenix, i3 Drug Safety, with the Brookings Institution and with others to develop a collaborative framework for implementing active surveillance in the near future. Their presentation will also note how the data, the methods, and the best practices for active surveillance are still in development and are still continuing to evolve.

While there are new opportunities, there are also some real challenges and obstacles to implementing better post-market systems and using them

to achieve significant improvements on our knowledge and use of drugs and other medical products. After this discussion of basic strategies for active surveillance implementation, we'll then to a series of topical panels on key challenges and possible directions for solutions. This includes issues of infrastructure and governance, how can this kind of effort be coordinated assuming that the best possible evidence on drug safety is developed and drawing on both public and private sources of information and analysis? How can it be sustained given the limited resources available to the FDA and the need to rely on a broad range of private-sector databases and expertise as part of the effort? We'll also talk about data and methods. How can data from a broad range of sources be used effectively for better detection of signals of important safety problems and following-up on these signals to determine if they are a real issue. What methodological issues need to be addressed with such large and sources of data most of which do not come from randomized studies where the

causal effect of the drug can be readily sorted out? And what opportunities exist for learning in new ways, perhaps by applying methods from other complex data systems?

We'll turn to legal and privacy issues. How can all this be done while assuring that privacy and security of patient data and addressing other legal issues related to surveillance analysis? We'll also discuss communication issues and the impact on medical practice of these new developments. How can the results of these analyses be communicated effectively not just when there are definitive results, that's really the easier case, but also when there are interim findings when an association between a drug and a safety problem has been identified or is suspected and is being actively investigated but the issue hasn't been resolved? How can the effective use of information in medical practice be supporting, and are there other key issues from the standpoint of consumers and health professionals that should be addressed?

That's a brief overview of the objectives of this morning's meeting, and I'd like to say a few words about how we're going to do it. This is about taking stock of where we are now on these important issues, what key challenges need to be addressed and how can they be addressed effectively. It's not just about answers, it's about discussion and it's about identifying some promising ways forward with the challenges we still face. In setting up the conference therefore we had several principles in mind. One was that a broad-based approach with presentations from a diverse set of perspectives was the best way to facilitate the discussion and facilitate moving forward. We do want to share some collaborative work that has been ongoing and that we have been involved with on these issues, but we mainly want to stimulate ideas that can be the basis for broad-based support and timely implementation in support of the FDA's mission.

Another goal was that we want discussion, not 10 presentations of talking points, and in

addition to asking presenters to identify key issues and be part of this discussion, we want input from all of you who are here today. We'll have roaming microphones in the audience and we hope that many of you will use them for questions and comments as the day progresses.

By the end of the session we'd like to identify some next steps for our own collaborative work and that of others to support this critical and urgent part of the FDA's mission as effectively as possible. We expect this includes some papers reflecting today's discussion as well as other steps to support the implementation of a fundamentally enhanced system of post-market evidence as quickly as possible.

Just a few other housekeeping notes before we get started, this event is being webcast live and will be archived on the Brookings website for future viewing. We have a number of press in attendance with us today, and I'd like to thank you all for joining us. And because we've got a lot to get through, I'd

like to remind our presenters to keep their remarks as brief as possible in order to allow ample time for discussion. This doesn't apply to you guys right at the beginning, but for most of the presentations we're going to be aiming for about 5 minutes or so for remarks so that we have enough time for open discussions and questions. Also for all of you, all of the slides being presented today and all the other conference materials will be posted on the Brookings website at Brookings.edu as part of the Engelberg Center for Health Care Reform's web presence.

So in advance I want to thank you all for contributing to this important and timely meeting. With that, it's my pleasure to introduce Andy von Eschenbach. The Commissioner has a distinguished career in academic medicine and public service. He was a leading in clinical cancer research at MD Anderson in Texas, he is the former Director of the National Cancer Institute where he was working when we first had a chance to collaborate together on projects in government. He now Commissioner of Food and Drugs.

Remember that old slogan for the Army, the toughest job you'll ever love comes to mind. The Commissioner has the privilege and the very serious and challenging responsibility of leading the implementation of a range of new initiatives at the start of the second century of the FDA. It's a critical time for Andy being in his post and again Andy, thank you very much for your service for the public.

Andy is going to going to be followed by Janet Woodcock. Janet is a true public servant. She has served in some of the most challenging career jobs at the FDA including Deputy Commissioner overseeing FDA's science initiatives and FDA's operations, and also as the once and now future Director of the Center for Drug Evaluation and Research. In this job Janet is on the point for implementing the key provisions of the FDA Amendments Act including the provisions on post-market surveillance that we're discussing today. We're going to first hear from Andy about the strategic context in which the FDA sees its opportunities now for improving post-market

surveillance, and then I think we're going to hear in more detail from Janet about the FDA's Sentinel Initiative and FDA's related initiatives on enhancing post-market surveillance and drug safety. So both of you I hope you'll use this as an opportunity not only to provide and update and perspective which everyone here would really appreciate, but also to raise questions to challenge those of us who are here today, identify areas where input from all of this could be useful for the FDA. Andy, thank you very much for being here.

MR. VON ESCHENBACH: Thank you, Mark, and good morning ladies and gentlemen. If you don't mind, I'm just going to stay here at the table rather than the podium because I really think it's much more conversational and that's what we really are looking forward to throughout the entire day.

I would tell you at the outset my principal role here this morning will be to introduce Janet Woodcock. As most of you already know, Janet has worked extraordinarily hard but also passionately

around this whole area of developing the Sentinel Initiative. So what we are going to do this morning as a team is she will give you a presentation of that initiative with the great detail and granularity that's important for us to understand as we look at the importance of the Sentinel Initiative.

What I'd like to do at the very outset is to set the stage for that presentation and perhaps even set the stage for the entire day's discussion. First of all to do that I want to comment on the fact that so many of you are here. I can't tell you how important that is because I do believe that your presence here this morning indicates that in this entire area we have reached critical mass. We now are at a point where we have been able to bring together all the parts and pieces. So if today serves to squeeze and compress those parts and pieces a little tighter so that the dynamic interactions between us become more intense and more frequent, then I truly think this can be an explosive time, a time when we can really make dramatic and radical changes in our

ability to use the delivery of health care as a discovery platform.

That's what this about. FDA is committed to this and Janet's passion for this is reflected throughout the entire agency starting with me and going down through all of the other parts and pieces of the organization. There are many people from FDA who are here today who will participate in discussions whether it's John Dyer (ph) or COO or Tim Stitley (ph) our CIO or Frank Torty (ph) our chief scientist and on and on and on because this is about something far more important than simply an initiative. We're not doing this at FDA only because Congress told us to do it. We recognize as Congress did the need to have a post-market surveillance system in place in order for us to have much greater opportunity to not just simply passively be receiving information about adverse or unexpected outcomes but, more importantly, to have an active system in place where we can get that information and that knowledge at the earliest possible time.

But that is not the only reason why we're doing this, and I would venture to say that in the end we will find it isn't even the most important reason why we're doing this. The reason we are doing it, must do it, is because we now have an opportunity where on the one hand sophisticated information technologies and infrastructure has been created. On the other hand, many of you represent and reflect parts and pieces of the health care delivery system where you now have the ability to gather data, information, about what is actually occurring in patients in the human condition when we apply interventions whether they're drugs or biologics or the use of devices. And by now beginning to put all those parts and pieces together we're being able to create in the delivery system a discovery platform that if we capture and appropriately analyze that data we will learn and understand about biologic mechanisms of disease and our ability to alter or change those mechanisms in a way that eliminates disease and preserves health. This is about transforming health

care far more than just being able to create a more elegant system for adverse event detection and reporting. That's what we're here today to do, to transform the future of health care and the health care delivery system.

To do that is going to require us to do that. It's just do it. I don't say that lightly because I do think that there are serious concerns and serious issues that have been raised about this initiative and I think it's important for us to draw a distinction today between doing it and using it. From the point of view of the FDA, we want to join you in catalyzing and accelerating the implementation of this infrastructure. We must do it and we must do it now. But that's different from using it to make regulatory decisions and we recognize that we are not there yet and it will take an opportunity for us to put this in place and apply rigor and discipline in our ability to understand the system and work through the system before ever using the system to make regulatory decisions. So I want to assure you at the outset that

we should make those concerns about how the data will be used to be an impediment or blockage for us creating the system in the first place. We can draw that barrier and that distinction. As we define doing it, that then should help us to understand that we will address issues of patient privacy and confidentiality, we will address the issues of the scientific accuracy and reliability of the data before we use it. But on the other hand, as far as implementing it, what we should be looking at today are not all the flaws or the defects or the blemishes that we are obviously aware of when one is looking at a system like this, but only see them from the point of view can you identify among them what we believe to be fatal flaws.

If we can identify the fatal flaws and address them, we should do that and must do that before we do it. But if it isn't a fatal flaw, it's just a flaw, a blemish or a defect, it shouldn't stop us from doing it, it may impair us or prevent us from

using it, but that's an important distinction I think I would like to see us have in our deliberation.

We have launched Sentinel Initiative and many of you had the benefit of being a part of that launch. Janet is going to explain that initiative to you now. FDA must, will, and needs to do it because it's the right thing to do. We look forward to working with you in understanding and continuing to learn how to do it in the best possible way. And most important then how to use it to protect and promote the health of every single American. I really appreciate your willingness to be here this morning to make that happen. Janet?

MS. WOODCOCK: Thank you, and good morning. What I'm going to do is try to provide some clarity about a number of issues because if we're going to have a substantive discussion today, I think people need to understand a variety of things, what FDA does now, what we're planning to do, and so forth. So I'm going to go over what FDA has traditionally done for medical product adverse event surveillance. I'm going

to be very brief, but I think we have a wide audience and not everyone knows exactly what has gone on. Then I want to talk about the changes we're working on now. Some of them are in response to the Amendments Act, some of them have been going on for some time. What is the future of safety surveillance over the next few years? And then talk about how we see the Sentinel part of this could be structured, not down into technical details, but actually what is this? What does it look like?

To start here, the mainstay of our current system is displayed up here. It's called spontaneous reporting and this has been in effect for a decade. What happens is the public sends us reports. We approve medical products, and I'm going to broaden this to medical products, our Sentinel team and everybody they're all across all the medical product centers, and actually for some of these things in the future we think foods and so forth that we'll be able to get reports of those as well, but for this time being, let's talk about medical products.

The public, the health professionals or patients report through the MedWatch program generally by paper right now, sometimes by phone to us, and then that's put into the FDA databases. The industry is mandated to report any adverse event they find out about and there's elaborate internationally harmonized schedules upon which those need to be reported. Those currently, a great deal of them are submitted electronically through what's called the FDA Gateway and then that goes into our databases as well. So currently these reports that we get even today, and this year are a mixture of paper and electronic, and we get hundreds of thousands, over 500,000. I haven't added them all up. We get a very huge number of individual reports every year.

Soon for drugs we'll be seeing all electronic we hope and then ultimately all the others will go to all electronic reporting over time. The way we're going to do this, on the left-hand side there it says MedWatch Plus. That's actually a project we're working on at FDA and it has two

components. The first is a front-end website so to speak that we're doing with the NIH and that will allow reporting of adverse events online by anyone, and it also would allow adverse event reports of clinical trials to the IRBs, and so that's the NIH piece of it. So we're going to provide a unified system for adverse event reporting because we've standardized the forms. Then MedWatch Plus, the box there, that's the back end. That's the processing system. We're in the process of purchasing a new system at least for drugs that will process this much more effectively than is the case now for drugs and then it will eventually be extrapolated to all the other medical products.

That's spontaneous reporting, and my point is that's going to continue to be an important part of overall FDA surveillance. That's not going to vanish or go away because we have these other ways of getting information. The problem with spontaneous reporting is in many cases we don't have enough information from it to know whether there's a

causal relationship between what was reported or not, and then we have to go investigate these reports in some other way.

But even now we don't stop here. We have other additional resources that we utilize and we have utilized probably over decades to perform surveillance. The Center for Devices has the MedSun program which is kind of an augmented spontaneous reporting. They're out in the hospitals soliciting reports to get entered into computer systems or in the hospitals about device malfunction in the hospital. And vaccines have a special system, VEARS, which is run with the CDC for vaccine adverse event reports and that was put up because of the indemnification of vaccines. But generally we have had contracts or at least other types of arrangements that I have here shown that allow us to get access to claims data and other electronic health data over the years and we've worked with academics and we've worked vendors. So the point is we have experience. We have a track record in the flaws and the benefits of using these

sorts of data, and we've been doing this for a long time.

We also of course on this right-hand side get information about performance of the products from ongoing clinical trials after the products are approved as well as registries and other things that are set up and these types of arrangements will continue as well. So it isn't as if we're putting all our eggs in the Sentinel basket and walking away from these other types of things.

With the passage of the FDA Amendments Act there's additional work going on that I want to talk about at least briefly and this is particularly in the drug arena. The Amendments Act had several sections on drug safety that Mark alluded to. One of them called for new authorities for FDA to implement and many of them were around the post-marking period, peri-approval and then post-marketing. Then it called for FDA to set up this active surveillance system as you already heard, and FDA is in the process of implementing these statutory provisions. With regard

to the new authorities and REMs and so forth and many other safety issues that have arisen over the last decade, the Center for Drugs for those of you who don't know at FDA is implementing a program called Safety First. This is really an internal program. We haven't made a really big external deal about this because it's what we're doing in the organization. The essential core of this program is an intensified focus on post-market safety so that we have increased organizational resources, tracking, project management, timelines, and so forth applied to the post-market safety programs the way we run our premarket use fee programs that have very strict management controls over them. So you will see the same level of scrutiny and performance and attention around post-marketing problems as we have brought to drug development over the years. This initiative has also brought clarity to our organizational roles and responsibilities and this is something that has been somewhat ambiguous at least to some over the years and we're very clear on who is going to do what and who's

in the lead for example on the Sentinel system and our Safety Office is in charge of that. We're implementing REMs and the other new authorities, there are certain recommendations of the Institute of Medicine and the GAO as well as the agreements that were made in the prescription drug user fee program this time around safety, there are other agreements made, so there's a whole menu of things that we have to accomplish. That's all been organized under Safety First and there's a large working group working on that.

Next year we're going to implement the next stage of this initiative which is called Safe Use. This will be focused on ensuring the appropriate use of drugs through partnerships with health care and so this fits in extremely well with our Sentinel concept because we're really going to have to partner with health care and have health care at the table to improve the appropriateness of how medicines are used.

What about the new surveillance provisions given all that? The first thing that needs to be

said, and Andy has already said this, is that these are really new approaches. We need to study them and engage in pilot activities to determine how they'll work and whether they'll work and how robust the analysis is. If you talk about the future now, we're engaging in pilots and so are other people and that's good news. There's a tremendous burst of activity going on. These databases are becoming available, the technological tools are getting there to access them, and all of a sudden it's just limited by our will and our organizational ability to actually start working on these databases.

The solid lines are things that are going on now. FDA is engaged in a pilot with CMS and this is a within-the-government pilot to see how well the part D data might be analyzed for purposes of determining safety signals in the population. We've been collaborating for some time with the VA and DOD. They both have electronic health records of different types and we're applying our data-mining system for example

to DOD and we'll see what kind of results we get back from that. Then we are engaged in other pilots.

Then in the public arena, we're going a research pilot through the foundation of NIH and this is called, OMOP, the Observational Medical Outcomes Pilot. That one is going to rigorously test various test methods of interrogating an assembled database. It's assembled data from multiple sources that's publicly available data generally. So that's going to be a rigorous test of methods and that's a big pilot that's also going on that the FDA is participating in and probably many people in this room. Then EHI (?) are doing pilots. I have a dotted line because we aren't members of those pilots, we're just working very closely with all the different groups that are doing this to look at the outcomes and see what's going on. Then of course another public-private partnership proposal has been announced which is Sentinel, and I have a dotted line there because it's not done yet.

My point is even as we move into the future, again, Sentinel isn't going to be the only program, but as Mark said and as Andy said, Sentinel is very special because we view that as the coming together of health care and the government to build something that really can be transformative, but that is going to take a trajectory for us to accomplish.

Now I'd like to turn to what potentially the Sentinel would look like simply so we can have some idea in our minds about what we're talking about here. I think the next panel is going to present another perhaps slightly different idea, and that's good, so we'll have a couple concrete suggestions on the table.

We at FDA under our Critical Path Initiative have been engaged in a lot of public-private partnerships over the past several years and they all turn out to have somewhat repetitive structures because there are only a certain number of ways you can do this. If you want to do a public-private partnership for Sentinel, we're going to require a nonprofit convener, somebody who can bring the private

and public parties together on neutral ground, and many groups are willing to serve in this way. That wasn't meant to be funny. Usually then you'd have a charter and the charter would embody the public document that would embody what actually the partnership was for, what it was going to do, what its boundaries were, what it wasn't going to do and so forth. So then you'd put together a public-private partnership under this convener, and from the FDA's point of view to tell you what we've been doing, we've been meeting with a lot of what we call the data owners, the people who have the databases. Many of them are health care systems. Some of them have commercial types of data. Some of them are practitioner networks. There's a wide variety. We have had many meetings and we've had a lot of goodwill around the interest in doing this, but also people want to see it written down, they want to see what exactly we're talking about, and I'm sure there are lawyers who will want to see it five times if my experience with lawyers is generalizable. There also

would be other partners and there are many other parties that would be interested and could join the partnership, and then the FDA could be part of this.

We could do this under the Reagan-Udall Institute in which case I think we could join this partnership if we do it under a nonprofit that is statutorily mandated to implement a federal mission. We're a full partner in the OMOP pilot, for example, and other federal agencies may wish to join this public-private partnership as well.

The public-private partnership then would get a governing board together and that would be part of the charter, who gets to vote and how, and how all that is done would be developed and made publicly available and open to scrutiny. This governing board or executive board or committee would probably have to have a staff, the consortium staff, there would be a director and other people who run the different programs of the public-private partnership. Of course, this one is really about research to a great extent. We're going to need a very strong scientific

advisory board of independent scientists who can vet and provide advice in both scientific policies as well as types of analyses. Then we'd need to have a contractor who ran the guts of it, the infrastructure of it and querying and so forth. Then we'd need to run the research program. We really feel as we go forward in Sentinel that it's important to put up the infrastructure and get that and just do it as Andy said and innovate as we go as we learn. But it's also very important to have that research arm from the git-go. We're looking and we're doing rigorous scientific scrutiny of what's being done and what's being produced and we can innovate, and we'd like to have fellows and individuals like that, young scientists who can really be working on this as an innovative project.

Here's a model of how this infrastructure would look, and I first have to say I shamelessly borrowed the little firewall pictures from Marcus Wilson because I think that's really good. The point is what we're envisioning is a system where we would

query but that the personal data would remain behind these firewalls, and this is technologically doable. We might have to put some money or contractors behind the firewalls under appropriate protections to get the data in the right shape to be analyzed and then sent out and those things would be worked out and all those types of documents could also be made publicly available so everyone could satisfy themselves that the arrangements that were made were appropriate and had the appropriate protections, and that's a query system with a distributed network.

On the other side of other data sources it was very interesting, we started out with thinking of a distributed network, but we had a substantial minority but vocal to all our meetings that we've held who say, no, we'd like to link more because patients go here or there or we have this piece of data, we don't have all these pieces of data, we would like to link. So I think there are also possibilities of exploring for example claims data lumped together or various linkages with registries and so forth, those

types of folks. These raise privacy issues a little higher and then would require to have all the appropriate protections put up in front before we went into any kind of linking, but we don't want to put it off the table because it may be something in the future as IT gets better that we could actually do.

My time is coming to a close and so is my presentation. I want everyone to start the morning with a clear idea of what we're trying to achieve and the fact also that we're not abandoning our other public-health activities that we have, this would be augmenting what we do now.

MR. MCCLELLAN: We have time for or two questions, and the topics that Janet and the Commissioner introduced are going to be discussed throughout the day today, so there's plenty of time for further discussion. But one or two questions now. Let's have hands up, and then do we have microphones in the room yet? Yes. So if you could raise your hand and then get a mike. Those two back there and,

again, we're going to have more time later for questions and discussions.

MS. SMITH: I do have a question for Janet.

MR. MCCLELLAN: I'm sorry, can you identify who you are and where you're from when you ask questions?

MS. SMITH: I'm Jennifer of "FDA Week." Just two cautions for you, and that is when it comes to the registers you're talking about, do you mean clinical trial registries, and what kinds of groups have asked for this? Do consumer groups have raise the issues about linking up those registries?

MS. WOODCOCK: The registry owners only have a slice of the pie. They only get a certain amount of information about the people and it might be possible in the future that you could consent people to allow more of their records to be linked to so you would have a fuller understanding of the outcome. For example, let's make something up. Say there's some brain thing that people have implanted to do something, they have some order, maybe Parkinson's,

and they have something implanted. The registry might capture that they had it implanted, but then they go off and they have experiences in other hospitals and nobody knows and you can't link up what happened to those people. Maybe they get psychiatric problems or something and that wouldn't be in the registry necessarily. So there's interest in having more information sometimes in these registries or be able to access more information so you would actually be able to help the people more who enter the registries in the first place. You'd able to help them more. But nothing like that would be done, as I said, obviously that would require a higher level of consent and transparency about what's being done and so we wouldn't do that to start, but we don't rule it out over the years that we're never going to do something like that.

MR. MCCLELLAN: One more question here?

MS. WEXLER: Sylvia Wexler, Union of Concerned Scientists. You mentioned in the Sentinel infrastructure the need for a strong advisory board of

independent scientists and I wondered what you were thinking and how you were thinking about conflict of interest in that advisory board in those independent scientists.

MS. WOODCOCK: All these boards and structures will have to have conflict-of-interest policies written. So I don't have in my mind right now what they would look like. That would be a collective process that would probably include the public. We're asked by Congress to be very transparent about all this so we would develop draft policies and get comment on them as we move forward.

MR. MCCLELLAN: Thank you. I'd like to thank again Commissioner von Eschenbach and Dr. Woodcock for joining this morning. Thank you.

Now while they're coming up I'd like to introduce our next round of presenters on Building a National Network for Drug Safety. As Janet mentioned, this will complement some of the ideas included at the end of her presentation. Again, the focus here is getting some ideas on the table for discussion to help

shape moving forward on these policy issues as effectively as possible. Joining us to do that will be Marcus Wilson, Rich Platt, and Janet Marchibroda. Marcus is President of HealthCore which is part of WellPoint Health Networks. He previously was the strategic research partner for WellPoint Pharmacy Management as a faculty member of the University of the Sciences in Philadelphia he developed an outcomes research on patient education division and this spin-off of this program was the start of HealthCore which works closely with WellPoint on issues related to surveillance and learning from the actual experience of its members.

Rich Platt is the Professor and Chair of the Department of Ambulatory Care and Prevention at Harvard Medical School. His research focuses on the epidemiology consequences and prevention of nosocomial infections, on infectious diseases, and pharmacoepidemiology including a large amount of work related to the use of HMO network populations and extensive electronic data to identify patters and make

effect interventions. His research has also involved developing consortia of HMOs for this purpose and he works with the search program that Janet alluded to earlier.

Finally, Janet Marchibroda is the CEO of the eHealth Initiative and its foundation which are both Washington-based independent nonprofit organizations whose missions are to improve the quality, safety, and efficiency of health care through information and information technology. Janet previously served as the Executive Director of Connecting for HELPA (?) a public-private sector initiative that was designed to catalyze actions on a national basis to drive electronic connectivity, and recently Janet has been doing a lot of work which Janet Woodcock alluded to before in terms of piloting some of the methods and ideas using electronic databases that could eventually be part of this active surveillance Sentinel system. They are going to do an overview of some of the issues and frameworks and expanding on some of the issues that Janet raised earlier, and we're going to talk

about it a bit. So I think Marcus, are you starting off?

MR. WILSON: Thank you, Mark. What we're going to put forth I think in a few minutes is a diagram that we think is a good starting point, and I think as a starting point I'm going to go back to one of Mark McClellan's first comments, that this diagram is not meant as the answer but the beginning of the discussion for a lot of the work we think needs to be done in terms of constructing this system as pointed out by Dr. von Eschenbach and Dr. Woodcock.

As we started this endeavor several months back to begin the construct of this diagram that we hope serves as the beginning of the start for the whole safety initiative we thought the most important aspect was to set forth basic principles for a system such as this so that as we make decisions both leading up to this meeting and after this meeting in terms of what this system ultimately would look like, that we make those decisions within the framework of these principles. The key things about or one of the goals,

and our goals are in four basic categories, one is we want to approve accuracy of safety detecting in adverse events, we want to improve the speed in which we do it, we want to improve our acuity especially in looking at the reality that risk and benefit is not equal between all populations, so if size matters in this case we ought to get to some of that acuity, and we want efficiency. We know that the current cost structure in terms of generating evidence in looking specifically at the clinical trial environment is nonsustainable when we get into this size of an endeavor so we have to make this something that the system itself can reasonably fund.

These principles that we set forth, one is as was pointed out early on, patient privacy is key. We always want to protect patient privacy and I think that has to be very close to all of our decision making. The other is that we realize that there's no one data source out there that holds all the answers, that has all the elements, that has the size you need in terms of detecting some of these events, nor does

it have representation from all the different populations that we know we need to understand in order to get that acuity we talked about. So we know we're going to have to put together complementary data sources.

The other is that there is one really important principle when it comes to using current electronic health care data and that is what we are talking about is the repurposing of the data. None of the systems that are out there were originally designed to do adverse event detection so what we have to do is be very careful on how we use these data for generating evidence. If you think about all the different data sources that are out there, each data source has its own idiosyncrasies, has its own nuances, and in many cases, many nonapparent -- factors. An example of that is even within our own Wellpoint data which represents about 35 million lives, we have tens of thousands of benefit designs, different benefit designs throughout those health plans which we're part of. Each one of those benefit

designs holds the potential to buy us the flow of data through that system. So understanding those benefit designs, potential impacts are very important. So as we think about this, one of the principles that we've put forth on this is that you need to keep the data close to its source because those are the individuals and those are the organizations that understand the data the most and they can help you interpret those data as those data are brought out for this purpose.

The other point that was brought out before, and Janet did bring this up, is that the claims data or electronic health record data, all the different data sources, one of the things we want to be able to do in each case is to enrich those data with other data elements that are complementary to that. So even in some of those environments that may be a node that we'll represent on this diagram, you want them to have the ability to get to other data when they need to. So if you're a health plan, you need to get the chart, if you're an electronic health record source, you need to be able to get to other sources of information such

as claims data on those same patients so that we can see what's going on in this. We also want clinical information to enrich those because that gives us better acuity in understanding what's going on.

The last principle that I'll expound upon here is that validating what we're seeing is really important both in terms of validating the algorithms that were used to generate signals, but also going from signal to validated event to try to assess causality is really, really important. So you have to have the ability within each of these systems to be able to validate on both of those domains. I'm certain that there are many other principles that could come from this group or to come from the audience that we need to highlight and hold near and dear as we make these decisions, but I believe this is again a bit part of that decision point.

With that, instead of focusing on databases, one of the things that we're trying to put is we need to focus on data environments and stay away from the database concept, although at least in the beginning

that doesn't mean we can't evolve to some of those aspects in terms of pooling some of the data going forward, but we need to understand those data and understand the processes and understand the strengths and weaknesses of doing those things before we move down that road. Our focus needs to be working to link together those complementary data sources to get us to the breadth and depth we need to in order to accomplish this goal.

To go to the diagram very quickly, and I'll point out a few things and then I'm going to turn the mike over to Rich and to Janet to take this further, one is to talk about the five nodes. The five nodes we have here, we're representing those as being data environments. The number is not important. Of course, there could be twenty nodes or two nods, whatever, but in this case those are the data environments that I was referring to before. Within each one of those data environments we put in the local analytics group. The reason that that's in there is because what you really want to start with is

working with organizations that have experience using that particular data environment to generate evidence because they'll understand not just the nuances of the data, but will understand how to translate whatever the question of the day is, whatever event we're looking for, into a process or a research protocol that will effectively generate that information.

The second part is to look at that network coordinating center. The concept is that that network coordinating center can have many charges, but it will be made up primarily of representatives from each one of those data environments and their job is to work collaboratively to help reach those goals of speed, of acuity, of efficiency, and accuracy. You also very well could that representation from other sources including the FDA that sit in that group as well to help provide guidance on this. But again, that for us would be the coordinating of many things including communications.

The third piece that I would point out is that this concept of the Sentinel System Coordinating

Center and that would be a body from the FDA. I think that could be very similar to what you pointed out as the convener. It could be something along those lines. I think it could have a number of functions, but it would have, and I think we've got the same scientific advisory board concept up there and I agree with your comments about that scientific advisory board and we think it would play a very important role, a critical role in all of this in terms of methods development, in terms of standards development, et cetera.

The last piece that I'll point out is this project research organization and project research committee. The idea is that on a given project, the FDA would make the decisions as to who to engage probably through a competitive bid process for a specific project. So it could be one of these local research organizations or it could be an outside organization that has the experience, the skills, and the talent to be able to conduct that project. The box below that is an important one. What we're trying

to represent in that particular circle or oval is that the project research committee would be made up of representatives from the research organization itself, other outside expertise, but very importantly, representatives from the research environments from which or within which that particular project is going to be conducted so that the insight, the local knowledge that's necessary to use that data environment is actually brought to the table for that specific project. That's the starting point in terms of the discussion. And again I think Mark I agree with you that these are not the answers, but it is something we want to put forth as getting closer to where we need to get to fielding that system.

MR. MCCLELLAN: Thank you very much, Marcus. Rich?

MR. PLATT: When embarking on a really transformative process like this it's helpful to know whether it's really going to be possible to make it work. I'm going to spend the next few minutes talking about some of the things that have already been

accomplished that I think give us reason to believe that this really can succeed and to outline some of the things that are going to be necessary in order to get from where we are to where we'd like to be.

First, there's a pretty good working demonstration of many of the attributes that Dr. von Eschenbach and Dr. Woodcock and Marcus have talked about, the faxing safety data link that the Centers for Disease Control operates that currently is operating as a distributed network of eight health plans with 11 million individuals that does prospective signal detection to assess the safety of recently marked vaccines. The things about it that are shared features with the network that we're talking about are that there are well-defined populations, that it combines electronic medical records and claims data that has developed and uses novel statistical methods that allow frequent updating of observations so you can find a signal at the earliest possible time. It uses distributed networking methods so that programs are developed

centrally and then distributed so that they run behind the firewalls, and personal information is protected because it never leaves the health plans. And finally there are knowledgeable local experts who work in partnership with the CDC and FDA in developing, implementing, and interpreting the protocols that are developed.

Several big questions for us can these kinds of activities scale up to the size that the Sentinel network needs to be? Will it work for drugs, a much more complicate set of issues that need to be dealt with? And can it work in environments that don't have complete data on both claims and electronic medical record information? I'll mention four things that are steps along the way in demonstrating the feasibility of that.

First, several of us, Marcus, Arnold Chen (ph) at i3 Drug Safety and several others are part of a five health plan consortium that's anchored in my department in which we're doing a post-marketing evaluation of the relationship between the

meningococcal conjugate vaccine and Giambre syndrome. These are large populations because we're trying to look for very small increases in a very rare outcome. The total population is 50 million. We're using fully distributed methods to analyze those 50 million lives. The data all stays with the health plans. And it's working. There's no reason that it can't scale up the kinds of methods that we're using.

Secondly, as part of a contract that we have with the Center for Biologics at FDA, we have done key informant interviews with the leaders of 11 public and private organizations that are responsible for the care of 150 million individuals and they've indicated that they have the technical capacity to participate in a distributed network and would in principle to be willing to participate. As Janet said, there are lots of things for lawyers to be involved in and many others to make sure that organizations' needs can be met, but at least in principle there's good reason to believe that it would be possible to build a network of the scale that we're talking about.

Thirdly, we've worked in partnership with FDA and the Agency of Health Care Research and Quality as part of one of the Centers for Education and Research in Therapeutics or CERTs to test signal detection mechanisms using sequential methods to identify signals associated with drugs rather than vaccines and our first efforts in doing that appear to be successful, that is, we have been able to use historical data to show that if we had been analyzing it in a sequential fashion that we would have been able to find signals that we know exist with regard to those drugs. So there is some reason to believe that it will be possible to adapt these methods. Finally, we've partnered with i3 Drug Safety to apply these kinds of sequential methods to very large claims databases and it looks as though they'll work. So there's a fair amount that we've already accomplished.

I'd say that there are at least eight important needs that we have to address in order to get to the kind of diagram that either Dr. Woodcock or Marcus showed. One is I think we have to be able to

show that we can do signal detection prospectively on databases that as Marcus said are created for other purposes and are being adapted for these uses. It's probably doable but it's not a straightforward thing to do, so I think that it's important to test these methods in a prospective fashion. Secondly, we have to develop additional statistical methods to allow us to do signal detection in an appropriate way and have better methods for distributed analysis. There are certain kinds of things that are still very difficult to do in a distributed fashion and we need to be able to accomplish that.

We need to come to consensus about the definitions of the outcomes we're interested in, that is, when spontaneous reports are submitted to the FDA it's clear that somebody has decided that a person has liver failure but we need to develop the conventions that us go to these very large data environments and say how do we find the individuals who have liver failure or renal failure or bone marrow injury, and so

there's work to do to develop standard definitions that have reasonable performance capabilities.

Signal detection is only part of the challenge because there are many reasons that the signals don't mean that there's really a problem with the agent. Those are problems with the way the data happens to show up, it has to do with ways that clinicians use coding systems which change over space and time, and finally, when a signal is determined to be a real association and can we believe the data, there is still going to be the important challenge of deciding whether the drug caused the problem or whether the drug is associated with the problem. That's not a new challenge, that's been a major piece of the FDA's work for as long as I've been active professionally, but I think that there's going to be a change in scale in the number of signals that are going to have to be evaluated and the speed with which they will have to be evaluated and our nation doesn't have the professional bandwidth to do that work now so

there's a scaling up of capabilities that will be needed.

I haven't talked at all about the fact that we actually need to develop the network architecture. See all those arrows? Those arrows are really an important set of challenges that it will clearly be possible to build that network that allows efficient and secure communications, but that's work that we have to do and it's not entirely straightforward. We need to develop the communications protocol that we've already alluded to. At what point do you communicate what information to whom, and the most important whom is us as a nation who need to have reasonable expectations that information that's developed will become available.

The final thing I'll mention is that I think we need to have a national conversation about what are appropriate uses of individual medical records that also serve a public-health purpose. I think that is most important with regard to the way we use Medicare data. The same day that the Sentinel Initiative was

announced there was a very important announcement that Medicare drug exposure data will be available and linked to other information about Medicare recipients making Medicare data instantaneously the very most-important resource that the Sentinel network will have. But it will really only be fully useful if there's an agreement that when there is a need that appropriately authorized individuals can have access to a very small number of full text medical records to confirm the specific outcomes of interest. That may mean that looking over millions of records that it's important to review hundreds to try to answer the question of whether a signal is a real event or not, but without that ability, it's going to seriously diminish the utility of that record. I bring it up as my final point because it's both very important and I haven't heard any real discussion about making that final link and so I think it needs to be on the high-priority list. I'll turn the mike over to Janet. Thank you.

MR. MCCLELLAN: Thanks, Rich. Janet, please go ahead.

MS. MARCHIBRODA: Marcus talked about the goals of an active surveillance network and some of the key components of a distributed network. Then Rich provided some examples or models that might provide some input or lay the foundation for moving this work forward and also defined some of the key questions. I'm just going to spend a few moments this morning talking about the availability of different data sets and different sources that can support the Sentinel Initiative while protecting patient privacy and confidentiality.

As noted, if you look in the Sentinel Initiative white paper as well as the various communication pieces and listened this morning, Sentinel intends to draw upon a rich set of data sources and there are many, many data types particularly now that are needed to support signal detection and validation in our country. Ultimately we think that Sentinel could draw upon clinical

information whether it's from laboratories or pharmacies, electronic health records and integrated delivery systems in hospitals, of course the growing number of health information exchange initiatives that are happening locally, and in some cases at the state level across our country and perhaps data from large physician practices all doing so in a way that carefully protects patient privacy and confidentiality.

I think in fact that these connections are going to be important because when you think about the long term, we're sending queries out to get information back, but then we're going to want to close that loop and begin to reach out to the care delivery system to provide information to those who work with patients every day.

The other thing and particularly in the last year we're seeing a lot of interest in personal health records. We've all seen the news around Microsoft or Google and even sites, consumer facing applications like Patients Like Me where thousands of patients with

illnesses are sharing their experiences. I know there's a lot more research that needs to be conducted, but thinking broadly about the end in mind, how do we leverage what works today and build upon that but keep the end in mind around this connected electronic infrastructure that protects patient privacy but gives us what we need to greatly improve not only the quality but the effectiveness of our health care system.

Hoping the wind is behind our backs and moving some of this clinical data forward is all the activity that's happening not only at the national but also at the state level. We're seeing a lot of movement on standards, identification, harmonization and adoption, with leadership by the federal government now moving into the private sector. We're seeing pilots emerge from CMS. We might just see some legislation that encourages in the early years through bonuses physician adoption of electronic prescribing through the Medicare program and thinking through that impact on the data that's out there.

What are some examples of using clinical datasets to support post-market surveillance or similar activities? I'm going to share some results of our Connecting Communities collaboration that Janet referenced earlier this morning for drug safety which we shared a bit at the last Brookings roundtable in January. We're focused on testing in two environments, both at Reagan Institute in Indianapolis and Partners Health Care system in Boston, a set of three use cases. The use of statins and liver toxicity is the first warfarin related bleeding episodes, and then a small set of DMEs, and we wrapped up in April our first iteration of testing. We wanted to look at three types of data, claims and lab, looking at electronic clinical data, to see if there were differences not only in the different data types but also in the different environments. What we found on the team, and there are some team members here in the room, we're going through our second iteration of testing right now to further validate our results this summer, but we are seeing that there are some

differences depending on the data types that you use whether if claims are clinical, and we're also seeing that there are differences in the environments. So what it raises for us, long story short, there is much to learn regarding the use of various methods and the usefulness of different datasets, all necessary and important, but thinking about how they fit together, and this is one of the key elements of the Sentinel Initiative, the public-private partnership, to create an environment to test methods by different organizations and initiatives and quickly feed that information back so we can all learn and get better to serve our nation's drug safety goals.

There are examples of the use of clinical data and particularly in distributed environments, and Rich talks about some of them. There are some others that are moving forward like SPIN (?) or ITB2 (?), clearly the work of the CERTs, and some in other environments like public health where there is some interesting work through an initiative called Distribute that is also moving this work forward that

we can learn from, and I think there is a great deal of expertise to draw upon as we move this forward.

In closing, I want to run through based on our experiences not only within the Connecting Communities Collaborative but in a broad multi-stakeholder coalition that's thinking a lot about how one connects data both within communities across our country but across the country in a way that appropriately protects patient privacy and some principles to think about.

One of the most-important principles and what I'm pleased to hear about this morning from the presentations is building and leveraging what's already been done and so I think we've got some near-term opportunities to just do it and to build on things that folks have done but also keeping the end in mind because it's a very heterogeneous environment out there. Depending on what data types you have in different environments, the standards that are being applied or not, even the proprietary nature of the data, and if you go locally across different states,

the culture around policies for information sharing are different. So what's going to be really interesting in light of that and given this environment, I think one of the most critical elements of building Sentinel is almost to create an addition to an electronic network, a social network if you will, that brings together the best and the brightest that is inclusive and it doesn't shut people out but brings people in to share their experiences about what works and what doesn't work. And also, and this is what I learned in New York last summer when we kicked off our collaborative, funny things happen when you get together informatics people with epidemiologists and folks who are safety experts from two environments, magic happens and the sort of brain power in the combination of sharing is really exciting and we were able to break new ground. Just imagine doing this on a national scale. So I think this notion of a social environment in addition to one that focuses on the technical aspects will really be important.

Some final points because I think we're getting ready to wrap up here is we're going to talk later about governance. I talked about the importance of inclusiveness. We already talked about the importance of a decentralized distributed approach particularly addressing head on issues around privacy and confidentiality and building those policies for information sharing into the front end will be very important.

Just imagine a collaborative learning environment that doesn't force one set of protocols or principles from the git-go but one which brings different disciplines and different experts from across the field to come together to solve one of the nation's biggest issues which is around drug safety and I am excited about the work that the public-private partnership with the leadership of the FDA can do to make this happen not only to address drug safety issues in our country, but even more importantly and what I'm very excited about is building this notion of an electronic health government infrastructure that

respects patients' privacy and confidentiality that can help us tackle broad issues in our health care system around quality, around effectiveness, around access in health care.

MR. MCCLELLAN: Thank you very much, Janet. I'd like to thank all of the panelists for their presentations. I'd like to open this up to questions and discussions. Once again if people could raise their hands with questions and we'll get a mike for you, and remember try and identify who you are and where you're from.

MS. : I'm Kathy -- from United Bio Source and this is a very exciting time I guess for epidemiologists. What I'm wondering is are we hoping -- people across -- environment? Are we going to have unique patient identifier? That's one question. The second one is as we do this, I would be tempted to try and get data standards in place because -- to try and standardize?

MR. : I'd say Sentinel network 1.0 will not attract across sources and that'll be okay I

think because there are currently more than 100 million people's worth of data environments in which there's at least several years of reasonably complete data for individuals. It's not everything and you could do better if you could link them, but it's possible to get this started without doing the linking across. So imagine how you would want to do that in version two because it would be important among other things to be able to link the kind of data that a health plan has with a vital statistics registry. Just -- into the National Death Index would be an important thing to do.

I'm talking about things I don't really understand, I'm an academic so that's okay. The Merkle Foundation's Connecting for Health Initiative is hosting a series of conversations about topics like how you can match across databases with neither data owner disclosing identifiable information. And so I'll say the magic word one-way hash systems that would allow a neutral convener to be able to say without knowing who the people are person number 67,

in your dataset is the same as person number 85 in your other dataset and then for an appropriate purpose like this particular investigation you could put that identifiable data together. So it won't be necessary to create a master patient index or to pool all the data even when you're putting the data together. That's in 5 to 10 years kind of thing that we'd handle I think.

MS. : I might add to that though I think we do have an opportunity in phase one of Sentinel to actually link patient data. In fact, that's precisely what we did in the Connecting Communities Collaboration in two markets, in Boston and Indiana, using a record locator service. We pulled data from many hospitals across the system, laboratories, physician practices, so I would say absolutely in phase one. I don't think it's something that could happen on a nationwide basis and certainly HHS is helping us move forward on standards to make that happen, but clearly it's happening in a handful of markets across the U.S.

MR. MCCLELLAN: Just to follow-up on that, we may talk about this a little bit more when we get to the data and methods discussions in a little while. Janet, the pilots that you've done that could be regarded as a data environment albeit it an integrated data environment where together at the regional level you all work out a lot of issues that haven't been worked out at the national level to permit a kind of richer database contribution to this effort nationally even though we're not really there on the national methods for doing that kind of linkage. Is that something you see fitting in with this initiative in the short term?

MS. : Absolutely, and I think Rich you mentioned Connecting for Health. Boston and Indiana, and I know that Rob Colladner (ph) is spearheading some efforts through design and trial implementations too, but 2 years ago we actually were able to test across two markets and do linking there as well. You have to deal with differing policies, privacy policies and that's hard, but it's absolutely

doable. Mark, I don't know if you want to say anything else about that.

MR. MCCLELLAN: Marcus?

MR. WILSON: There's not much to add to that because I think you've made the main points, but one of those principles that I talked about early on that we're thinking about is an ability to enrich the data and part of it is enriching in the current environment in which the patient's in, but the point about being able to bridge data across systems as patients move through the data over time, I think that's an important spot to get to and I think it's something that we have to aspire to.

MR. : There's one more thing. You asked about standardizing. That's going to be a huge piece of work. Even to have age mean the same thing across datasets, take nothing for granted in how much fighting through the swamp the actual implementation is going to be, it's important not to underestimate how much ground-level data element by data element discussion there will have to be to put together this

sort of very high-level concept. I think for that reason 1.0 is going to need to get started on existing standards. Medicare claims represent a lot of people and so I think a standard industry kind of claims definitions are going to be the place to start and even then it's going to be quite a considerable amount of work to make the stuff be reliable.

MS. : But you know what? The interesting thing about standards, Sentinel also offers an opportunity to help us get to an interoperable health care system so while we don't start there, if you look at the work that CMS and what we're doing on quality, we're beginning to embed standards to help drive the system to our ultimate goal which is interoperability.

MS. : I think this is key issue, but it is more of a longer-term issue. I agree with Janet. What we're hoping is that we can come together as a sort of research community on this. Then we can help incentivize and help enlist people in the need for standards because people will see how they will

benefit them in the analyses they're trying to do and that usually is the biggest motivating factor, if something that's going to do something for you.

But it's clear talking to NIH that if we're going to get the genomics revolution nailed down we're going to have to have thenotypes understood. A thenotype is like an epidemiologic base definition of some sort and until we have all that, what we really need to do eventually is to link the finding to some hard science, to some basic science about why the problem happened to those individuals. And until we can define actually what they had at some greater level of specificity so we can subset them, we're not going to be able to do that. So the basic science research community I think will also be motivated to start getting these definitions in place. If we can enlist them in that effort once we get this started, then I can see us moving into a standards effort in a more substantive way.

MS. : Ana -- from FDA. I'm trying to add the point of view of somebody who touches the -

- the way that I see it, we need to reduce the uncertainties that we have when we are finding safety signals. And how can we do it? How can we be sure that something really exists and how reproducible that signal is? This is similar to -- I'm old enough to have seen how difficult it was to access clinical laboratory data in the beginning of my medical career because there were not standards in place and -- process, we set up standards. Standard data it takes us 5 minutes to load the data into a standardized tool and start analyzing it versus -- how many months it could take -- data, et cetera. But we need analytical tools -- great standards in theory, I am sure that we are going to lose. It's very important that ground work but we need also systematic tools in place because then we will be able to understand which are the missing pieces. If there is -- process and to be able to analyze more than -- issues, there are some low-hanging fruits to be able -- I'm not paraphrasing Norman's talk which -- that he's saying which are the

most important safety problems that we need to deal with and to do it in a systematic way.

MS. : Rich or Marcus might talk about the analytical methods, but let me go back to the social environment example. What would be so interesting is we run a query, someone finds something. Let's say we've got 100 organizations in this social environment network. Number seven find something. We're not sure, so you reach out to the other 99 and they run it also and you share your methods and then you figure out whether this is really something. And this can happen in this environment quickly in a way that FDA can evaluate the impact of the different environments and the methods and maybe you get somewhere faster and with more certainty, but Rich I'm sure --

MR. PLATT: One thing that I think will be extremely important, to pick up on your point, Ana, is that we need to protect this enterprise from throwing off false alarms that will diminish its credibility. I think one way to start doing that is to agree at the

outset that only certain kinds of questions will be asked at a first pass. That is, rather than say we'll sort of blindly look for every association that could be there, we'll say we will only look in an organized way for signals associated with the most common causes of serious drug-related problems. So that's the list of designated medical events. For each drug or drug class it might be a small number of additional things for which there's reason to believe that you need to be on alert. And otherwise you would use this system to confirm questions that arise from other sources, if a spontaneous report system or an independent study or a clinical trial raises a question, you could seek to confirm it, but not to use it as a source of unguided data mining. Even if we do that, I think that it's going to be a very important challenge to get to the right level of being sensitive to signals that exist and not being diverted by things that prove to be a false alarm. We've seen in the vaccine safety data link the potential risks of finding a signal that takes a while to sort out but in that period between

you're not sure that it's not a signal and an obligation to report, there's a potential to really erode public confidence in the immunization system and so there's a real challenge.

MR. : Just one thing to add to that. There are two parts that I think really could be big problems with the system if we don't address them early on. One is false positives which we talked about and I think if we go at it with purpose in any specific endeavor I think we can minimize that. The other part of it, it was mentioned but it really hasn't been talked to any great extent, but it's a task that we have to take on very quickly in this process and that is to lay out what's the communications process for signals when we see them, who will communicate to whom and when and I think that's something that we've talked about in many forums including with Janet and her team. We have to lay that out because I think that it could be one of the biggest risks. It could also be one of the best ways to mitigate some of the issues we may see when we

see a signal in how do we actually go from signal to validation very quickly but also in the mean time how do we mater that communications process.

MR. MCCLELLAN: This is a great setup for the next panel. There was one more question here I think. Two more questions real quick. Go ahead there and here.

MR. GORMLEY: Glenn Gormley (ph) here now with Geminex (ph). Let me link into the last comment, and Rich to pick up on your point of bringing the public along with us. One of the potential derailers of this process as I see it is the public one day wakes up and realizes that their data is being used by people who they don't know and understand and in ways they don't understand. Then the people who think they represent the public have their own agendas or issues. How do we engage the public along this process and who represents the public? Who would we talk with so that there isn't a sudden waking up? And when we get to the point where all this becomes operational, the public sees it as a good thing for them and not

something to be afraid of because of not understanding it.

MR. MCCLELLAN: Let me just add that we are going to come back to this after the break.

MR. : My 10-second answer is we need a broad public conversation and we should frame this as a public-health activity, and we already have the expectation that for appropriate public-health needs that public-health agencies have access to patient level data.

MR. MCCLELLAN: One more question right here.

MS. : -- from the Army. Two points. Our health care is getting more expensive and I presume everybody else's as well. A couple of the things that we're looking at are as you know Medicare has provided us with new codes that help us look at certain laboratory values such as A1C (?) being greater than 9, you actually have an -- 9 code and some other information in there. But the difficulty for us as a medical organization is that maybe a

couple years before contracts are in place and we pay the additional price for additional coding. In addition we're looking at investigating enriching claims data with actual laboratory data, but the price of that also is high. And I didn't know if any other organizations are pursuing trying to ask for labs to be brought in with their claims data, and if you do have that experience, how did you prioritize the labs that you wanted to be brought in? And secondly, how much did that cost you to bring it in? Also what kind of patients because clearly if you ask for everything, you're going to pay for everything. Thank you.

MR. : There are many efforts, many organizations, including ours that have successfully brought lab result data and integrated it with claims data. We can talk about it more -- if you'd like, but the process is not an exact one. It's not inexpensive. And often you have to make sure you're getting the rights labs attached to the right other -- as well. So that process, there are good ways to do it, there are organizations, many of them including

our group that have the same types of things that are out there and I'm sure there are many places you could go to to talk to you about how they did it and what it cost to get it.

MR. MCCLELLAN: It sounds like you guys should talk. I know there are more questions. We're going to have some more opportunities to address them after the break. I'd like to take a short break now. We're going to reconvene at 10:45. Thank you all very much.

(Recess.)

MR. MCCLELLAN: What we're going to move to now is a more detailed discussion of some of the challenges and opportunities challenges and opportunities that come up around the implementation of this kind of public-private active surveillance network and how it fits into some broader issues, broader issues at the FDA, as Janet mentioned its regulatory activities are above any beyond what's going on in this network, some broader issues in the medical community around developing evidence and other

steps. We're going to start that with a brief discussion of infrastructure and governance issues. I've asked the speakers here, Janet Woodcock who you all know and who was introduced before, and Garry Neil who's the Corporate Vice President of COSAT, the Corporate Office of Science and Technology with J&J.

MR. NEIL: Still with J&J.

MR. MCCLELLAN: Still with J&J. Yes. We had some other changes that we were talking about earlier. I want to make sure I don't get things wrong. You got to stay up to date here. What I've asked them to do is speak for just a few minutes, 4 or 5 minutes, on teeing up some of these particular issues in more detail. We're going to do governance and infrastructure first and then turn to a set of other issues all of which I think resonated with the questions that we were starting to get and the comments that we were starting to get earlier this morning, so hopefully we're going to build right on to that. Garry?

MR. NEIL: Thanks very much, Mark. First of all, everybody got one of these when you came in. Janet has produced a really fantastic summary of these issues on governance and I would encourage everybody to really take a very close look at that.

The remarks I'd like to make, in general when you're talking about issues of governance it really boils down to who decides, who does the work, and who ends up paying for it. So we are going to have to come to grips with it. None of it is particularly easy and we're looking for I think a lot of input or FDA will be looking for a lot of input from all stakeholders on how best to address those issues.

From an industry point of view, this is a really exciting time and it's also a really great opportunity for all of us I think because I really feel that we are present at the birth of a true revolution in health care. A lot of that has already been talked about this morning, but it's enabled by the convergence of technology, culture, and of course

need which precipitated a lot of this. When we look at the power of information technology, emerging science, genomics, biomarkers -- biology, all of that, and applying it to the challenges that we're now facing, it really underscores the need for us to try to address these issues by, one, focusing on training. Where are we going to get the people with the right training to be able to carry this out? So I think one of the governance issues that we need to address is creating a structure to engage with the health schools, the schools of public health, the medical schools, nursing schools, and wherever to make sure that we have a real supply of well-trained epidemiologists and quantitative scientists who are going to be able to come in and really implement this, and they're really in very short supply and there are a number of things we could do so I want to see that that is emphasized.

The very nature of this enterprise really must be predicated on science, on rigorous science, and scientific principles so we definitely need as has

already been talked about strong, independent scientific board and committee to help oversee all of this. I also see it as an historic opportunity for us to really engage with many of the stakeholders, this has already been alluded to by Glen and others, on what this means scientifically. This debate about drug safety and product safety and food safety even has somehow been couched in terms that aren't really scientific, maybe they're more religious or philosophical, but as some sort of titanic struggle between good and evil rather than really a focus on science and what it means to use powerful contemporary products that have enormous capacity to help patients and have enabled us to benefit many people's lives, to extend life in this country, but also have the capacity to harm some people and to create side effects, but we need to have that discussion around benefit and risk. So I think one of the elements of governance that we also need to address is communication and education. We need to do a much

better job of that and we are really in the spotlight here.

I also hope that we could try to attract scientists from any adjacent disciplines, whether that's sociology, economics, astrophysics, wherever, people who are really engaged in the study of data and trying to make sense of data because we again are creating in my view a whole new science here. Science has often been advanced by the intrusion of people from adjacent disciplines coming in and bringing their knowledge and insights and so we really need to do that. Perhaps the creation of some sort of a committee or formal group that could encourage them would be useful as well, and those are a few thoughts that we had.

We also want to remember that we need to involve FDA and industry scientists in there because we have tremendous insights that we bring to the table not only on safety surveillance but in the long term, and this has been alluded to over and over again, the fact that if we're doing this right we can build a

national treasure if you like, not only a repository of data, but a place where people can come to train, to learn, to work and to develop and revolutionize the entire health care system so we can bring products to the market that are more effective, that are safer, and that are less expensive. Some of the insights that we gain from that, associations, yes, that's important and is there causality for a safety issue is very important too, but what additional insights can we gain about what's happening in populations of people, not animal models and not just individual observations, those have been very important in the history of medicine, pharmaceutical medicine and all sorts of medicine, bringing those insights from the clinic back to the bench and then using that for new target discovery and finding new and better ways of doing things. We all have many examples of that in our own careers. So I think having those scientists engaged with this is really very important too. We'll have to figure out how to do that, whether they're just involved in the protocols, helping looking at the

tables, whether or not really manipulating the data, but getting to some of those issues in a way that we don't exclude them because there is much more here than just drug safety.

I also feel that we need to do something to engender some culture changes among the physicians and health care providers, some practical suggestions. The -- that have been talked about, the PHRs, they're not designed today with this purpose in mind, so what can we do to make them serve that purpose better and what can we do to be able to train physicians if they would provide some input around causality to us, if we could end up in a system where we had an automatically generated MedWatch how much quicker could our progress be in this area, and so some of that is going to have to be engagement at that level with the provider community and with those who are actually creating these instruments that are going to provide input. So again it's a great opportunity and those are some of the thoughts I had.

MR. MCCLELLAN: Thank you, Garry. Janet?

MS. WOODCOCK: I'm going to be short. What I've provided here is really kind of a to-do list. Resolve these issues.

MR. MCCLELLAN: This is standard operating procedure for Janet.

MS. WOODCOCK: I've already heard -- conflict of interest, obviously that is in our minds and has to go on the list. Also I think we're going to hear maybe in the next panel about patients and making sure they have a very broad role and input in the context of how this system operates, maybe some formal role, and so we'll hear more about that. I think that's a very good suggestion.

The reason I wrote this to-do list down is not that we've settled any of these, we haven't, it's to make sure that we have a long enough to-do list that is inclusive enough that we don't forget any of the things that we're going to have to keep in mind. So that's what I'm hoping this discussion will bring about. Obviously the governance of this is very important. Everyone is going to have to trust that

the governance will be in the interests of the patient in the health care system so I think the governance will have a large representation in my mind from those data owners, the people who are actually seeing patients and the people who are responsible for patients, and of course FDA and some others. But I think the role of the patient community and even the health care professional community has to be worked through more and to what extent are they involved also in the governance because they're very major stakeholders as well. But all different issues, intellectual property, communication polices, conflict of interest, all those obviously will have to be dealt with. As we said very explicitly as we move forward we just want to make sure that our list is very complete and we don't have any really glaring omissions.

MR. MCCLELLAN: Thank you, Janet. Questions and comments? Have people had a chance to digest Janet's list yet? Some good topics.

MR. HILL: Jeffrey Hill with the American Medical Group Association -- Data Warehouse. I think we all and even in our data warehouse where we're looking at ways to improve the process of care and understand better ways toward quality, we of course said, yes, and this could be used as part of the Sentinel network likewise and appropriately so. In putting together the Sentinel network this infrastructure could be used for a lot of other things, looking at outcomes and performance perhaps.

One of the issues we deal with I didn't quite see on the list here, and I apologize if I missed it, was what do you do with these datasets that are so tightly controlled when you do see an event that might be suspicious that then becomes validated or extrapolating to the broader scope of value when you have outcomes data or quality data or perhaps performance data that comes out of this on a certain segment of the industry or a certain specialty of care or a group of physicians or perhaps even a specific physician practice? Is there then a sharing of those

results or perhaps an identified dataset to those individual so they can see the basis of those decisions or those analyses in the case of either a medical products company whose product is then at risk or the practitioners of medicine, not just their patients, but the providers who are helping to generate that some of whom may not be involved in all of that data that was generated, it might be scattered? I think that might be something we need to be thinking about.

MS. WOODCOCK: If you move under scope of activities on this list to the last bullet under scope, we talk about what the partnership should be involved in and what it might be involved in. These are not fixed in stone whatsoever. None of this is fixed in stone. I'm just giving my opinion here. The infrastructure that we build that will enable queries could be used for other queries outside of medical product performance which is what we're building it for though. So if we build an infrastructure like this, it would be a waste to have other people build

another infrastructure to do similar queries for other stuff. However, I don't think this partnership which would be with the FDA and those providers should get or be responsible for managing the results of queries such as about quality. Are you following me? But it could under contract or whatever that the infrastructure could be shared but then there would have to be some other group that was doing that that had the appropriate policies. The infrastructure is neutral in a way. It's just an infrastructure. So I believe that quality or performance of all these other things should be governed by some other governance structure than the Sentinel network. That's what I believe, however, they might share the same infrastructure.

On the other hand, I think your point is we could incidentally discover things as we're doing our regular queries because we're going to see disparities in outcomes amongst different groups that have reported back. That's good. We have to put that on here because we have to deal with it once we find it.

One of the ways a network like this would add value -- why would anyone join this network? If they get results back. If they get feedback. Nobody wants to give poor care. So if they're performing way below everyone else and we see it, then we would give it back. As far as quality of the medical products that we're actually surveiling, those communication and data policies would be governed by the consortium and that would be open within the consortium and the communication of that would be governed by the protocols that we've all been talking about developing. As Dr. Platt said, we need to avoid alarming the public every day or we'll have to credibility so it has to meet some type of credibility threshold before there would be public communication, however, we certainly would look at those within the consortium. I have one more thing, I'm sorry this is long, but this is a very complicated question.

MR. MCCLELLAN: It's a good question.

MS. WOODCOCK: As we're thinking about this at the moment, each member group that has data that

they're sharing would be able to opt in or opt out of doing that. If they opt in to participating they're going to buy a little bit of risk for themselves as well as the benefit. In other words, they're going to find something out maybe about their health care system and that would be governed by the data-sharing policies that would be in place, so they would know that in advance.

MR. MCCLELLAN: A question here and over here.

MR. SHIFF: Gordy Shiff (ph) now at Partners in Boston. We heard about network 2.0, 1.0, actually I think network 1.0 has a lesson that we should be thinking about which is sort of pre the one that we're talking about. Speaking as a practicing physician and the fact that I can't get the list of medicines that my patients are on, just this question about what medicine someone is on, and that lists exists, so somebody has it. The drug rep has it. IMS complies this data, but I actually don't have it to practice better care in the office, should tell us something

about the cart driving the horse and building on Janet's comment about where the data should be come from and be owned and the sense of ownership. So to draw on that as an analogy and think about doing it right in this as we move forward, this really has to be oriented around making it better and easier to practice good medicine while at the same time giving the health research community a sense of what is really accurately -- I should be sitting there working with the list and refining it, working with the people. At Cook County Hospital where I worked, we had access to the transactional database for our patients. They all got their medicines for free at our hospital and we knew when their medicines were filled, what they were on, and we could work with that. It's sort of an example of this public system being so far behind and we were ahead. So we just contract have to think about that.

Then I'll just add that related is you asked about we need more information about causality. We need causality about why people are being started on

the medicines. So get that indication, to get that diagnosis in there not in a way that tells doctors you're just going to have to do one more thing whether you like it or not, but to really figure out how to integrate that into the work flow so it actually facilitates things. For me I have this vision of touch and voice, touch screens, nobody has to tell people at the airport to use those touch screens. You could wait in line and do it the other way, but if somebody has just really thought of streamlining that into the work flow and integrating it makes it easier and obviously the data probably is very accurate in what's captured at that point of service. So this has to be driven by the horse and not the cart here in some fundamentally different ways.

MR. MCCLELLAN: A very good point. Janet, it builds on your comment about incentives for participation, even more front and center about goals for improving medical practices, a key motivating part.

MR. : And it's even more complicated because we don't have the over-the-counter drug use data either, and maybe PHRs ultimately will help you get at that.

MR. MCCLELLAN: I don't think we shortened your list of topics, but as the discussion goes on we'll see what we can add. I'd like to thank Garry and Janet for introducing these two topics.

We're going to move right along to some introductory comments on data and methods issues from Arnold Chan who directs i3 Aperio which tracks newly approved prescription drugs in real-world use as part of Ingenix and the United Group. Arnold provides medical insights with his medical background and oversees i3's research and reports are generated. He's a former epidemiologist who has studied drug devices and vaccine safety using large databases like the ones we're been talking about today throughout his career.

I also want to introduce Gigi Hirsch, the Executive Director of the Center for Biomedical

Innovation at MIT whose mission is to improve patient care worldwide by providing a safe haven, a place where academic exports, government, industry, all stakeholders can work together to develop new ideas that can be applied to some real-world health care challenges, and we certainly have our fair share of them to discuss this morning. Arnold, please go ahead.

MR. CHAN: Thank you. This is a graph from the FDA report, so when we talk about data inevitably we have to say something about the bubbles and the circles -- I'm just going to start with an example just to follow-up with what Dr. Platt used this morning about the Sentinel system 1.0. This is pre-1.0. This is a study funded by the FDA related to a risk-management program surrounding a specific drug. That was a drug that was not supposed to be used by some people but then despite the FDA warning and warning from the manufacturer, you didn't really change medical practice. So Dr. Platt and I were both involved in this study.

What I highlighted was the -- came out in 1998 but the paper wasn't published until 2000 so we definitely could have done better if we had a much more efficient system to address the same questions. So this is not a direct it causes harm question, but it has to do with it could potentially cause harm for a specific group of patients.

So if we had a better system today, l what are we going to do? I'm just going to touch on three points because I only have 5 minutes. Basically this is the first one and kind of a philosophical one. Raised several times before along with the discussion of the development of the Sentinel system is that now we have exhausted 150 million people who could potentially provide data for this type of activity, then you lose the ability to validate the signal. So if we think along the lines of signal of risk identification and then risk evaluation, then we'll be stuck. What I propose here would be for example going back to the circles we use circle A and circle B for risk identification and then take circle C and circle

D for risk analysis, and with apology to Marcus, I used the term database and I should have used the term data environment. Or with the technology that we have I think a better way would be to use 50 percent of all the data or one circle and then to keep the 50 percent for the potential risk evaluation, and the technology is definitely here.

My second point is how to get data from disparate data sources. The example that I share with you, the paper was published in "JAMA" in 2000, we did the same thing although we didn't spend a lot of time doing this because I was part of the research team that extracted the data from our system and the data for that particular study came from several data sources, several of us who are in the same room today. There could be several ways. There could be the same protocol and then within each bubble the knowledgeable data analyst within each bubble develops the data. That's one way. Another way is what Dr. Platt mentioned with regard to the -- is that you have the same protocol and then each of the data environments

will build a similar or identical data structure so that the same set of -- could guarantee that you will have a similar set of results so that the discrepancy would not come from the discrepancy of the data but could be a real signal that could be identified from multiple data sources. As we moved along with the current development of the methodology, it could be done in a virtual manner rather than in a physical manner. So instead of putting the data and massage it into a physical database, the technology is here such that we can do it in a virtual manner. Some of these points have been pointed out this morning so I'm not going to repeat that. I'm just going to emphasize the last one because everyone said it, security, is such that individuals and systems can control who can have access and who cannot have access and there is an audit trail that this query came from the FDA, it was approved by the FDA, and -- on the medical records of these 5,000 patients and only on these five data elements. So the technology is here such that an audit trail can be revealed.

As Garry said this morning, it's not just from the schools of public health, but actually some methodological development came from computer scientists. I'm not going to name the name of this particular company, but it is well known to be a powerhouse in computer technology, and some folks in San Jose, California, just developed this whole concept of a database such that individuals can have individual control over what data elements can be accessed. And the same can be applied to the data sources, so there are two levels. One is the individuals who say Arnold Chan I don't want my HIV status to be known to whoever, so there's one level at the individual level. And then at a higher level, United Healthcare would say all these United Healthcare employees, the data cannot be accessed by whoever, so there can be two levels. What I do know is that this technology has been imported into the health world as well.

This is the last slide. Now that we know there are technologies to get data from heterogeneous

data sources, then the next step is how to combine them. The simply way would be to aggregate data a the table level and just combine the tables, or have the identified individual level data to be combined. In practice it could be done the first way, say you have aggregate data from each circle and it can be combined in an analytic process, and the second then is to have the -- dataset combine them and you can do complex analysis. The real challenge that Dr. Platt mentioned this morning and I'm going to touch on is how to conduct very complex statistical analysis in a distributed manner. I don't have an answer.

MR. MCCLELLAN: We'll let that fly. Gigi?

MS. HIRSCH: Good morning. Thanks for including me in this discussion, Mark -- really appreciates it. I just wanted to start by saying a few words about what we see to be the priorities in this area of tools and methods -- are old hat to you. But we believe that we need to get a point as quickly as we can to develop a set of best practices in this space and that's going to involve rapidly doing pilot

studies looking at existing methods and in some cases we will most likely to create some new methods. Then we need to as quickly as possible get to a share understanding of when to use which methods alone or in combination with others, and that's going to depend to some extent upon what the question at hand is and what types of data are available to answer those questions. That's a lot of knowledge that we have to develop as quickly as possible.

In order to do that there is definitely a need for more research funding in this space. Fortunately, new funding sources are being established which all of us are grateful to see. In addition to that, because a lot of the questions are so cross-disciplinary in nature, it's very important to have forums where we can be doing collaborative research and health care and having collaborative discussions across disciplines and that's going to be a big theme of what I mention here today. That's why what Mark is doing here is so very important. These forums are rich opportunities for those discussions and we do

similar types of things at CBI in terms of our research approach.

In the longer term -- talent pipeline is very, very important in this emerging field of safety science and I'll pick up in a second on what Garry mentioned just a few minutes ago. In addition, we also think it's very important to see the excitement of this, that as the new platform and knew knowledge and capabilities will be established for safety surveillance, this is a wonderful opportunity to leverage our investment in these activities and to try to figure out how we can harness those improvements to improve R&D and patient care as well. So this is indeed the beginning of a revolution of sorts.

At CBI as Mark said, we provide a safe haven for collaborative research across industry, academia, and government. This is slightly different from what you've been seeing. This is our multi-petaled flower that we see as representing the landscape of safety systems. At CBI we are focusing on the petals of the flower which are highlighted in blue here. There is

one particular theme that we are pursuing at MIT in this space as we try to figure out the best way that we can contribute to this important area, and that is that we are working with faculty who have knowledge and tools from other industries but have not yet worked in health care. We are in the middle of a sort of real-time vetting and translational research process to see how these types of expertise from other industries might help.

Specific examples, in area of signal detection for example we are working with a faculty member from civil and environmental engineering who has developed a very interesting software system. He calls it a 911 data trawler which looks at trying to identify early signals of patterns across individual 911 phone calls that might allow you to identify at an early stage for example a terrorist attack, and we believe there might be some interesting transferability to the early detection of safety signals using this software system and his approach.

Another faculty member that we're working with has done a lot of work in financial services and has used lots of different types of statistical methods from operations research which we think may also benefit safety surveillance.

In the area of risk management and benefit risk communication we're working with a couple of faculty members from the aerospace industry. One has done very interesting work looking at risk modeling of complex systems, and another one has done work in the area of enterprise architecture, lean manufacturing and systems transformation which we believe could be applied either at the provider level across a single organization or a provider system or potentially across the industry where there are multiple stakeholders looking at these safety issues.

Finally, we just launched a new initiative that is a future scenario development initiative. The thinking behind that again is that we're going to be very optimistic and say within the next 10 to 15 years we are all going to get this figured out and in 10 to

15 years we're going to be in a very different place and the world of drug safety is going to look very, very different. We are taking this opportunity with some of our stakeholders to take a look at the strategic implications of what's happening in safety surveillance trying to understand how some of those may interface and converge with developments that are happening environmentally and in other technical areas to reshape the world of drug safety and we will then use that to identify a near-term research agenda that we think might positively influence the way this world looks.

Just a few words for a moment about a talent pipeline. Being at an academic institution, we think a lot about this sort of thing. Because we've been in an interesting role in this space within MIT that is trying to recruit faculty and students to focus their attention on this, we think that perhaps there might be some leverageable lessons that we are learning from this process. I'll just throw a few of these out there and would love to dialogue more with folks after

this. What we're finding is that when the faculty look at research opportunities they have a way of looking at it in trying to decide which opportunities to pursue. In general they're looking for multi-year funding opportunities. At the senior faculty level there is an opportunity cost associated with switching from what they know well to a new space even when they really, really want to do it. At the junior faculty level we've had the experience of a tremendous junior faculty member who started to dive into this safety surveillance stuff with is, was very excited, and then his chairman told him that he needed to shift his focus to the world of energy because there was a lot more funding available to pursue that. We also have heard from faculty that the level of complexity of these issues that we're looking are so challenging that you really need Ph.D. level research to really generate the quality of knowledge that we're looking for here. Another issue to consider is that junior faculty who are looking for tenure, their tenure opportunities are going to want research problems that

will draw very, very talented graduate students. And also the cross-disciplinary nature of this type of research has its challenges and risks for academics. We have done a lot of cross-disciplinary educational pathways at MIT, we're kind of familiar with the life cycle of establishing a new cross-disciplinary educational pathway, and it's challenging for them because sometimes it enjoys a somewhat lower status than traditional academic pursuits. But nonetheless we are finding a tremendous amount of excitement at MIT and we're looking forward to doing what we can to contribute here. So thank you very much.

MR. MCCLELLAN: Thank you very much. Now I'd like to open up some discussion around the data and methods issues that Arnold and Gigi have teed up. Again any questions or comments? Just raise your hands when you're ready.

MR. : Thank you very much -- from Novartis. I'd like to follow-up on one of Arnold's slides. I think it is a good idea to not pass the signal coming from the same data environment, whatever

terminology. So you basically propose two scenarios, either A, B, C, D, or versus a fifty-fifty split. I think either way has pros and cons. But there are couple of things actually that need to be considered. Number one, when you talked about the communication of follow-up signals, when you split the data A, B, C, D, the signals may not be consistent in the first place because there's always a chance finding that A shows a signal, B shows no signal. What is the decision in terms of follow-up? Actually if you do follow-up and use database D and C and B, the findings could be also different, one is positive and another is negative. So the question is number one, communication at the -- stage, the way you need to have a consistent finding and a validation of the finding before communication or not. I think that question -- the panel -- maybe Dr. Janet Woodcock also can comment.

The second thing is the formulary. New drugs coming to the market, different health care systems have different penetrations. That also comes

into play in terms of data selection for detection and for validation. Thank you.

MR. MCCLELLAN: Arnold?

MR. CHAN: Epidemiologists love controversy. We are very experienced dealing with results from different studies that do not disagree with each other. So to go back to what Dr. Woodcock said that there needs to be an independent advice kind of scientists kind of without any conflict of interest evaluating these signals according to their explicit predefined rules. So I don't want to go into the details, so I agree with you in general that there needs to be very explicit, defined rules to evaluate what is a signal and what is not.

MR. MCCLELLAN: Thank you. I think what we're seeing is as these possibilities for larger and more complex data analysis open up that there is a real need as Gigi mentioned in her comments for some major further developments methodologically to deal with them and I hope we've started that discussion of

highlight where that needs to go. There's another question here.

MR. : I'm Bill -- from Face Forward, Lincoln Safety Group. We'd like to really emphasize how much I agree with both Gigi and Arnold and the idea of having to open up this pipeline for research and for getting new people in and also the complexity of analyses. Some of the earlier charts seemed to indicate there would be all these different databases and then anyone could query the database. The word query seems to indicate kind of a simple thing but in actual fact a true new analysis might involve setting up an entire software system platform inside the database having possibly even a different database schema in order to make searches and certain analyses more possible. That would seem to imply a kind of close connection, an ability within each data structure to be more open to some kind of publicly accessible version of the data.

Also the ability to attract new researchers is often related to the openness of the data. There's

a kind of open-source attitude that can produce an explosion of research if in fact it's easy for people to get access to the data because without access to the data a bunch of people with theories of new statistical methods but without a way to check them and to modify them constantly is kind of almost impossible and not going to be very productive.

MR. MCCLELLAN: Just to be clear, you're advocating for as these processes get developed that there is a set of mechanisms for transparency around the data and the methods that are being used for analysis?

MR. : If it were possible even to supply a multi-gigabyte open-source data test platform where more people could have access to try out different methods as opposed to what I'm really worried will happen is that each data source will kind of make one contract with one researcher and without the open access that would probably be more productive because we just do not know the best way to analyze this data yet.

MR. MCCLELLAN: Any comments?

MR. CHAN: This is more of a governance data access issue rather than technical aspect so I will leave that to the --

MR. DENTE: Mark Dente (ph) with GE Healthcare. Part of the way we can address actually understanding the needs of data is to look for existing data standards. Part of the problem with our world is that we actually have too many standards so it's one of data harmonization and looking at the Office of the National Coordinator and CCHIT and maybe this organization and our efforts getting into those use cases so we start to understand -- has already been worked out so you have interoperability and also drives down the technical need of setting up your own database and data schema.

The other comment is just in support of Gigi. We've had great success across domain seeding of folks coming in so we've actually taken our own aerospace folks -- we make jet engines and we looked at low-signal detection in a jet engine to see if the

aircraft actually has to land in real time and we took those same statisticians and had them look for signal in our own clinical database and it was a wonderful experience with new perspectives. So I just to say, yes, we need to encourage people to come in and push us around and challenge us.

MR. MCCLELLAN: Thanks for the comments. One of the issues that has come up with the work of -- and its future course is a lot of interest in trying to help the standards activities focus not on the standards themselves but specific applications that really can motivate getting to practically relevant solutions on standards harmonization and it seems like these kinds of efforts could be a big help with that. Did you have any other comments? I'd like to thank Arnold and Gigi again.

MS. WOODCOCK: With regard to the governance and the topic about the test databases, some pilots are actually directed at this. So in year two we'll have better information because we don't know whether we want totally do just distributed networks and have

a lot of barriers to analysis. So once we've completed these pilots over these next several years, we'll have a much better idea about -- of course I think to have innovation we're going to have to let researchers have access to some of these datasets and we're going to have to figure out how to do that.

MR. MCCLELLAN: Thank you all very much. Next we're going to hear from a couple of experts on legal and privacy issues. These have already come up repeatedly this morning and you'll get to hear from some of the most experienced and thoughtful people on the topic. Kristen Rosati is a partner at Coppersmith Gordon Schermer & Brockelman. Her practice concentrates on clinical research, electronic records, health information, privacy, security, and consent issues. She had done a lot of work in this area as part of the American Health Lawyers Association and Health Information Technology Practice Group, is a member of the National Governors Association State Alliance for eHealth, and a range of other initiatives

on the legal issues related to the topics we've been discussing this morning.

Judy Kramer is an associate professor of medicine in the Division of General Internal Medicine at the Duke Medical Center where she is doing research activities including being principal investigator of the Duke Center for Education and Research on Therapeutics, the CERT program there which we've alluded to already focused on cardiovascular disease and she continues as a co-investigator there and also collaborates closely with the HMO Research Network. She is a member of the FDA's Drug Safety and Risk Management Advisory Committee and was recently named the Executive Director of the Clinical Trials Transformation Initiative which is another public-private partnership under FDA's Critical Path program. So Kristen and Judy, I'm not sure who's going first.

MS. ROSATI: Thank you very much, Mark, for the invitation to participate today. It's been a really exciting and interesting day. It's really fun

to be involved I think for all of us in this very cutting-edge activity.

You heard earlier from Janet Marchibroda about the eHealth Initiative Connecting Communities for Drug Safety Collaboration. The collaborators wisely realized that it's not just technical issues that we're dealing with obviously in creating a drug safety surveillance network, but there are obviously legal issues and public communication issues and a lot of other issues as well. So the collaborators asked my firm to look at the legal issues for health information sources, health systems that have electronic health records, health information exchanges and -- that are developing across the country, and the pharmaceutical companies involved as partners in a drug safety program, and asked us to produce two major things that might be of assistance to all of you going forward. One is a legal guidance that evaluates all the major legal issues involved in using electronic health information on the clinical side for drug safety programs. And second, a series

of agreements that hopefully will assist the partners in a drug safety collaboration with dealing with some of the contractual and legal issues.

Moving to the guidance, my understanding is this is going to be posted on Brookings' website so this is available for you. It's a very large document. I commend you to read the executive summary and then if you're really glutton for punishment you can go further than that. But we examined a number of different issues. Privacy obviously floated right to the top as one of the most important issues that we all need to deal with in putting drug safety surveillance networks and Mark has asked me to focus my comments on that today, so we'll spend some time on that.

But just to let you know what other issues are covered in the guidance, we also talked about common rule compliance in terms of all the research issues that you need to be dealing with, the FDA reporting obligations for drug manufacturers which is a real key issue here in terms of determining the risk

of pharmaceutical in participating in these types of networks. Obviously the FDA Amendments Act of 2007 had a very large impact on this whole area. Then finally we looked at tort liability issues under the common law for failure to warn. This is where the public communications issues that are going to be focused on are a real key player in terms of how we handle the legal risk involved for both pharmaceutical companies and the other partnerships in the drug safety network.

What our overall conclusion has been is that the legal risk is not high for health systems, health information exchanges, and pharmaceutical companies who are participating as long as there is very rigorous attention to the privacy and security of the health information. That's really a no-brainer, a very intuitive conclusion I think, and it's nice to see that a lot of attention is being paid to this through talking about the use of a distributed data network. I think that's very key to the extent that's possible to get good information out of that. And

then also the use of deidentified data when possible or partially deidentified data when possible is a real key to privacy compliance management.

Again on privacy I think this is just such a key issue for drug safety surveillance programs because there has been such public attention, a lot of pending legislation that addresses privacy issues. Just yesterday in "U.S. Today" you probably saw the article on personal health records and the public-privacy concerns with that, so clearly privacy is an issue that we need to pay close attention to. I know from experience in the health information exchange world and the development of regional health information organizations across the country which by the way have the potential to harness enormous amounts of good clinical data for use for public purposes such as drug safety surveillance, health information exchanges or RIOs (ph) are really struggling across the country with the policy issue of whether to permit the use of the data that they hold or that they have access to for purposes beyond the treatment of the

individual. Clearly everyone realizes that there are very important public purposes such as drug safety and other types of research for harnessing this information but it's difficult politically for HIEs and RIOs to make that conclusion. So I think the development of a national framework to guide that policy discussion for HIEs and RIOs is really key so that we can get to the point where we do have a national framework to support the delivery of health care as a discovery platform as Dr. von Eschenbach said earlier today. It's very key.

On the privacy front we looked at a huge variety of different federal and state privacy laws that any drug safety surveillance program will have to deal with. HIPPA is the obvious one. We also looked at the federal Part 2 regulations which govern substance abuse treatment information, the Federal Privacy Act, the Medicare conditions of participation, and then we also looked at the issue of state confidentiality laws which is going to be a real

challenge I think for a national drug safety network to deal with because state laws are different.

What we did in our report because we didn't have the resources to do a 50-state analysis is looked at different categories of state laws that generally provide greater levels of confidentiality protection than the federal law, particularly genetic testing and mental-health information, and HIV and communicable disease law and provided a framework for the analysis of these issues.

With all privacy issues, how that privacy evaluation comes out depends a great deal on the specific facts about how a drug safety program is put together. The HIPPA status of the collaborators, who has access to individually identifiable information if at all, and what type of information is utilized will all be really key factors in determining privacy compliance for a drug safety network.

I wanted to share with you just a couple of conclusions that really floated to the top in our analysis of the privacy issues. The first conclusion

is that the FDA will be really an essential partner in drug safety surveillance programs. That's obviously an intuitive conclusion, but when you look at particularly the HIPPA privacy laws and the state confidentiality statutes, involving FDA closely as a collaborator in these programs will be a way through the maze of privacy laws we deal with in two ways. One is HIPPA and many state laws permit the release of information about postmarket drug safety issues to entities regulated by the FDA, and, significantly, also to entities acting under a grant of authority from the FDA. So one real option for privacy compliance to comply with HIPPA and the state confidentiality laws is to have FDA delegation of authority or partnership with an entity such as the nonprofit convener that's being talked about to govern the distributed data network for pharmacovigilance.

The second conclusion that we drew from our research is that a drug safety surveillance program structured as a research protocol or a series of research protocols will also comply with most of the

federal and state privacy laws. In order to make a drug safety surveillance program work as a research protocol it will be necessary to ask an institution review board to waive HIPPA authorization, because of the large number of individual records that will be accessed to do these protocols it won't be feasible economically to ask for the authorization from individuals. And most IRBs because of those practical considerations probably would agree to waive the HIPPA authorization as long as again there's really rigorous privacy protection in place.

This conclusion has a couple of potential barriers along with it. One is regulatory uncertainty about the distinction between public health surveillance in human subject research, and Judge Kramer is going to be talking about that issue. Then the other real practical barrier to utilizing research protocols in a national network is the need to approach data source for institutional review board approval, and what that does is introduces potentially a large variability in IRB approaches and decisions

regarding the protocols, the privacy protections, and the other human subject protection issues surrounding that.

One way that we can address the IRB variability issue to perhaps to create a multicenter or a central institutional review board at the national level to provide primary review for these protocols and to provide local guidance to IRBs in the event that they want to do their local expedited review of the protocols as well. So while there are barriers to our way through this maze of privacy laws, they are barriers that we can overcome with a lot of coordinated effort at the national level. Then I'll turn it over to Judy.

MR. MCCLELLAN: Thank you, Kristen.

MS. KRAMER: Good afternoon. I would like to try to look at the implications of the regulations, the common law, the FDA regulations and privacy regulations from the perspective of a physician researcher, really asking the question of whether we're really protecting patients in the end.

In order to prepare my thoughts in advance I had to make some assumptions about what was the scenario I was describing, so I had to look ahead to what might be said at this meeting and hopefully I'm not too far off. I was thinking in terms of a range of goals for pharmacovigilance. The first everyone agrees we need to be looking for these designated medical events everyone talks about, the previously unidentified but rare and serious life-threatening events that we're concerned about no matter what the drug is on the market. But there's also a need as everyone knows with the recent events in terms of Vioxx and other products to detect an increased incidence even of common serious or life-threatening diseases like heart attacks and these things may have different regulatory implications in terms of privacy and how we handle them. But the underlying purpose as I see it if we think about it is to preserve the public health. This really is a public-health mandate. So the model I was envisioning is pretty consistent with what people talked about today, a

national system, a Sentinel system, taking advantage of electronic claims and health records using distributed data. I was assuming with 100 million lives that we're talking about large volumes that's required under the Amendments Act by 2012. And also a point that Rich brought up which is that we really need to recognize that validation will require limited access to complete medical records by the covered entity presumably.

So the first question is, is this research? I actually, even though I'm looking at this not as a lawyer but as a researcher, after reading about this it really appears that there are some conflicting interpretations. On the CDC, the Centers for Disease Control, website there is a guidance that is very clear and it seems very reasonable that if your primary intent in what you're doing is to protect the public health then it's not research. However, then I found a paper written by Edward Pritchard (ph) who is as I understand it the Acting Director of the Office of Human Research Protections which clearly

contradicts that and states that primary intent should not be used as a basis to distinguish from research from nonresearch. So the first thing we need to do is get some rationalization of perspectives to help people in these endeavors.

But Dr. Pritchard goes on to say if the public-health benefit of what you're doing is so compelling as to require participation, in other words, there are some thins where if everyone doesn't participate you won't get the right answer, if you're looking for the consequences of pregnancy exposure, somebody opting not to provide you the information completely undermines your ability to get the correct answer. And yet the practical implications of making this all a requirement are significant and I think would require quite a public discourse.

On top of there not being a consistent interpretation of what's research or public health surveillance, by the way, I did read the executive summary and then was compelled to read some more of Kristen's document and I recommend it highly, but they

point out that many institutions have internal policies requiring IRB review of all research conducted at the institution even if the research is not covered by either the common rule or FDA regulations and even when the research is exempt. So best laid plans of mice and men could be brought down by conservative interpretations and so this has to be a new paradigm or a social network where people are supported in different decisions.

Other issues adding complexity Kristen mentioned which is the confidentiality laws of multiple states, I do want to say one thing about FDA reporting obligations because the document that Kristen mentioned does state that expedited reporting would be likely required if you uncovered individual events. And I would just like to say that if in fact that were required, it would really add tremendous administrative burden without additionally informing because you're going to be getting aggregate data with a numerator and a denominator and hopefully creating an environment where you also could apply hypothesis-

driven research that has methodology to truly get at the base of what is going on.

The last thing that I really must pull into this is the possibility of false signals and we really must keep in mind the limitations of observational data. Researchers always think about this in terms of the big ones confounding by indication, for example, and this is the kind of thing that requires that we do hypothesis-driven research and not just count numbers and think that we have the correct answer because we are not protecting patients if we misinform in the end.

I think we also need to rethink the way that in the past we've handled duty to warn through a learned intermediary because I think now that we're dealing in a different world of these large databases and the quantitative methods that are used, we know for a fact that physicians do not come out of medical school with any understanding of how to interpret these types of data. In my view, we might have to move to a concept of an interdisciplinary team with

epidemiologists and statisticians and clinicians and FDA safety experts to actually have a discussion about what these signals mean and a plan prior to communicating directly to practitioners and patients.

So after all my reading, first I'm going to summarize what I think are the likely requirements under existing regulations and interpretations, and Kristen has talked about some of them. I think there is probably going to be a need for IRB review of all pharmacovigilance programs probably with expedited review and hopefully with central IRBs, but you have the problem that not all IRBs will defer to a central IRB and not all organizations will agree to that. There will likely be waiver of consent for large observational studies for all the things that are already in the regulations in terms of minimal risk and practicability, et cetera, and I doubt that that would affect patients' rights and welfare. We believe that the public-health exception in HIPPA for designated medical events would probably cover public-health surveillance of those types of events, and for

those things that require observational research, you would probably have a waiver of authorization. Again the use of full medical records being required I would think would be best handled by the covered entity being the one that actually does the medical record review.

But I want to go beyond that. I want to say that's what we would require under the current regulations and interpretations of the regulations. So the question is let's go beyond that and think about a new world. Those regulations and interpretations were developed before we used these methods. We're not just talking about disease reporting to CDC where the physician is sure that they've got a disease and then they just report it. We've talking about using an ICD9 (?) code that we're not sure of. So let's imagine a structure and a regulatory framework that actually recognizes the public-health benefit of pharmacovigilance where we have that discourse that someone talked about today with the public to explain if you're so concerned

about safety, realize that no drug when it's put on the market is safe. We know this. Let's not pretend that FDA approval means assurance of safety.

Then let's have a structure that recognizes the current state and the possible future states of health information technology as we look to new regulations, that we recognize the need for rapid hypothesis-driven studies to evaluate possible associations of serious events in a product, that we need rationalization of state and federal requirements for confidentiality in pharmacovigilance programs. And I think that the best minds should collaborate on how to facilitate pharmacovigilance and how to best communicate with patients and practitioners whether it's under current regulations or whether we have to write new regulations, but a lot could be done to actually deal with just the interpretation and get support for a consistent interpretation, this always thinking about the patients and public health not just protection of names. Thank you.

MR. MCCLELLAN: Thank you very much, Judy. We have time for a few questions.

MS. WEST: Sue West from RTI International. This was a very interesting panel because I think the legal ramifications of what we're doing are going -- the devil is in the details and that's where we're going to be held up.

One of the things I'd like to point out is that we don't want to be recreating the wheel. I just returned to RTI from UNC and when I got to RTI in January I found out that RTI had a project that was like a $16 million project with OR (?) looking at privacy and security across all the states. So what they've actually done is gone to all the states and found out about their privacy and security laws and I understand that report is either in development or should be available now. So let's use the things that are out there that have been funded especially by other government funders.

The other thing that I'd like to point out, and this is something that we've grappled with for

years for claims analysis, we know that the drug data is actually fairly good because it's based on dispensing data. We're always worried about the diagnoses because of upcoding and those sorts of things. But I was a health information technology meeting yesterday where somebody brought to my attention, our attention, that there could be issues related to use of electronic medical records and that physicians to protect themselves against medical malpractice may be altering their electronic medical records when there may be certain problems. I had always said the electronic medical record has to be correct because of practice reasons and now we have to start thinking about the electronic medical record electronic medical record could have problems as well. So I think we just have to keep all of these things in mind as we move forward.

MS. : Just a real quick response to that. Most electronic medical records systems have safeguards built in so that when the information is changed, the original information is still retained.

So electronic medical records actually are much safer from the quality perspective than paper records.

MR. MCCLELLAN: Any other questions or comments? Thank you all very much for the presentations.

I'd now like to introduce our last panel on communications and impact on practice, and we've got three very interesting perspectives here. Marc Boutin is the President of the National Health Council. This is a membership organization representing many areas of health care from many different patient advocacy perspectives. Marc throughout his career has been involved in health advocacy policy and legislation. Before joining the council he was the Vice President of Government Relations at the American Cancer Society for New England and he's also been a faculty member at Tufts. We're also going to hear from Sharon Levine who is the Associate Executive Medical Director at the Permanente Medical Group of Northern California. She is a board-certified pediatrician and a nationally recognized expert and frequent speaker on issues of

health policy and use of drugs and design and effective delivery of health care services. She also serves on the board of the Reagan-Udall Foundation. Lee Rucker to my right is a strategic policy adviser with AARP's Public Policy Institute. Her expertise centers on the appropriate use of medicines on medicine communication to the general public, on utilization management, on benefit system design, and a number of other issues related to ensuring value in pharmaceuticals. Do you all have a preferred order for speaking? Marc first.

MR. BOUTIN: Let me thank you all for having us here and actually I'll say I'm going to do something totally different. You've been sitting here listening to a great set of presentations and they've been logical for that half of your brain. It's time to go to the other half of your brain so you can give one half of your brain a rest for a few minutes.

What I'd like to do is address this topic from the point of view of people with chronic conditions. As we all know, we have unprecedented

access to information and our current decade is increasingly defined by public demand for transparency. We press our regulatory bodies for greater and greater access to information often with little or no thought given to implications on health outcomes of real people.

Consider for a moment a child named Adam Todd who lives in Cedar Rapids. He's an 8-year-old boy with severe epilepsy and he's endured up to 100 seizures each and every day. Epilepsy can be much disabling for some people. For this child the condition was truly tragic making it impossible for him to participate in even the most routine of daily activities, school, sports, play dates, social events. His life was at risk and his quality of life was absolutely terrible. His parents working in close partnership with a team of doctors tried more than a dozen medications and have finally found a drug that actually works for this child. Their son can now attend school regularly, he goes to birthday parties, he's actually on a basketball team, he has a normal

life. But there's a catch. The medication that he takes has an FDA black box warning because of serious effects it causes for some people, and as we all know, this kind of warning could have a major impact on physician prescribing, pharmacy availability, and certainly patient adherence to taking their medications.

As we develop new models to better identify and understand postmarket evidence we need to truly consider the impact of the disclosure of this information on public health. Adverse event data delivered without context for bias or statistical significance is likely to cause many people to stop taking their medicines and suffer the debilitating effects of their chronic disease or disability.

Our research at the National Health Council has shown that the manner in which patients assess benefit and risk is extremely complex. Decisions about medication generally involve both emotional and analytical factors including their prior experience with the drug, the severity of their condition,

symptoms, experience and trust of their doctors, and the credibility of information sources. We know the number one reason why people do not start or continue their prescribed medications is fear of adverse side effects. While we wholeheartedly support the creation of a national network for post-market drug safety, we want to ensure that any new evidence is communicated responsibly. Solving this challenge is complex, and we've had a lot of discussion about that today. But what is critical is the involvement with people with chronic conditions and their representatives.

Collectively we provide credibility and perhaps even more importantly context to this issue. Far too often, adverse events are framed from the point of view of somebody without disease or disability, someone who has never relied upon a medication to improve or extend their lives. Our involvement can persuade people to look through the eyes of a patient with a debilitating chronic condition, a patient who is willing to take a risk on an often risky medication for a shot at something

equivalent to normalcy. We can provide balanced pressure from the transparency advocates who courageously seek broad disclosure without considering the unintended consequences of others.

If you, your spouse, your mother, your brother, or your child stop taking their medication to treat their heart disease, diabetes, or cancer due to incomplete or inaccurate post-market information, we all lose. I think we need to ensure that Adam and the millions of other people suffering chronic diseases receive information that they can understand and act upon to improve, not harm, their lives. So the suggestion I would make to this group is that when you look at this chart, and we had a great chart put up by Janet earlier and we had a science committee to one side of the body, it ought to be a committee that has people with chronic conditions not to control the governance, although we certainly along with all other stakeholders ought to be at the table in the governance, but there needs to be a committee that can look at how we communicate the issues we're going to

find, and it also needs to provide perspective on not only the safety and the need for the medications or issues we're looking at, but it also gives context to the previous discussion about privacy. So often privacy is framed from the point of view of simply having your information protected and even people with chronic conditions want their information protected and with good reason, but remember that the issue of privacy is always in the context of the circumstances and if you're living with a chronic disease as are over 100 million people in the United States, the context of that privacy is important. We want to ensure that our information is utilized for research purposes not only to provide better medicines and treatments for us, but want to ensure that there are better treatments for our children and for our families. So one of the most motivating reasons why people are interested in electronic personal health records is because of the potential to use that data for research.

So allow us to help frame the context of this issue to give a lens through which people who may be perfectly healthy can truly understand the implications of these issues. Thank you.

MR. MCCLELLAN: Thank you, Marc.

MS. : Good morning. Dr. McClellan thank you much for including me today.

I'm glad Marc Boutin mentioned we're going to take a little different direction here for the next few minutes at least. I've brought some art. I think we have certainly heard this morning that, Toto, we're not in Kansas anymore. From the consumer perspective if think back to many, many decades ago what the consumer might have experienced walking into their corner pharmacy where the chemist probably knew them by name and probably saw them regularly and maybe around town as well, and at the time this painting was done the physician -- was extremely limited, but they probably had a good feel for the information about the drugs that they indeed prescribed. We will excuse the fact that this actually is an Edward Hopper painting,

and if you know Hopper, there probably was no communication going on between the parties involved, but we'll just pretend that there was. This painting was done 80 years ago, in the late-1920s. Fast-forward to today's system and this is just a schematic of our drug distribution model, and I wish I had earlier this week -- Tom Rice, the health services researcher presented on research pertaining to Medicare beneficiaries' choices pertaining to Part D plans and I wish I had his schematic because this makes this one look very bare.

What indeed are consumers experiencing in today's world when it comes to drug information, and I suggest we have Jackson Pollock. But it's not just consumers who are experiencing Jackson Pollock. It's everyone. It's prescribers, it's pharmacists, it's the researchers, it's all of us struggling with the past-market evidence.

As was mentioned earlier we do have assumptions that as consumers we all go in with in that we very trust our physicians, the prescribers,

our pharmacists and the FDA, we assume that our physicians will indeed know everything else that we're taking and that they'll talk to each other if we'll seeing multiple prescribers, we assume that our pharmacists do know the OTCs that they just sold us last week and how that might interact with our news prescription, and we do trust the FDA, and the signs were out there about the tomatoes so we do hear about the medicines as well. So those assumptions reign supreme in the consumer's mind. There is an oasis out there that may or may not be recognized, the balance between risk-benefit is perpetual motion like this lovely Calder sculpture at the National Gallery of Art, but that is something that is very challenging for consumers.

And there's a wonderful opportunity through communication. I love this quite from Dr. von Eschenbach from several months ago, "Our relationship with patients must be built on trust. That trust comes from communication and dialogue. It's not important what we say, it's what they hear."

With communication at mind, just a few quick ideas as to how we can move forward. I was glad to hear that Dr. Gordy Shiff mentioned a few minutes ago in a question that he is struggling with not having in his new home base good information about exactly all the medicines that are begin taken his patients. At AARP and many other organizations in this room and the FDA we all have out there developed lovely medication record forms. For example, I would love to see a medication record form in the Medicare new handbook, in the Part D explanation of benefits, when people are alerted to it's time for your welcome to Medicare physical, I'd like to see a rack of them in the pharmacy and in the physician's office. I recently spoke to the Consumer Health Care Products Association regulatory conference and they asked for outside-the-box ideas and I said my idea is inside the box, I'd like to see a medication record form tucked inside the box.

Another idea, there was a reference by Dr. Kramer just a minute ago about the need for better

training in pharmacoepidemiology. I think there also needs to be a geriatric pharmacotherapy curriculum in the medical schools, in the nursing schools, and in the pharmacy schools, as well as CE programs in geriatric pharmacotherapy for professionals already out in practice.

Many of us in this room, and I say us because we are a broad coalition, the consumer world has been launching programs to promote medicine safety for consumers. Several years in my former life with the National Council on Patient Information and Education we had a great campaign when the OTC drug facts label came out. We did a public-service announcement with Dr. McClellan and others, and the National Consumers League is here and they have their SOS Campaign, the National Council on Patient Information has something called MUST for Seniors, Medication and Safety Training. So these programs are indeed out there and I believe that it really takes a village if you will to borrow from one of our former

presidential candidates to help patients understand just even the basic level of safety.

In this age of freely available information, drugs cannot easily be parsed into safe and unsafe categories. There will be shades of safety that must be graded against shades of efficacy. This was a quote from the "New England Journal" last July 2007. I think that this concept is very, very difficult for consumers to understand and we really need to work all together to help consumers understand what part of that Jackson Pollock painting is most relevant for their situation at that particular time. Thank you.

MR. MCCLELLAN: Thank you. Sharon?

MS. LEVINE: Thank you, and I am humbled by your artwork. My assignment from Mark was I have 5 minutes to reflect the concerns about communication and impact on practice of 600,000 physicians practicing in the U.S. today who have an obligation and a responsibility to understand issues around drug safety and to communicate that effectively to their patients.

I want to speak first kind of in a global sense and then get into some of the specifics that I think are having today a significant impact on physician practice and some tremendous opportunities as we move forward as we sit on the verge of transforming practice. As many people have said about electronic records, it's more than just digitizing paper records. It is about creating an opportunity to understand what actually happens and to transform not just the safety and quality of care but also the way care is delivered to meet the needs of very different generations and for those of us who trained to practice medicine 30 years ago were led to believe are life was going to be about.

The first and I think most significant issue is one that Lee spoke about and Judy Kramer spoke about which is in fact there will always be uncertainty about the safety of any product that is regulated by the FDA. It will always remain. Our job is to get a lot better about limiting and constraining that uncertainty. As Lee said, in the minds of the

vast majority of consumers, and we've done focus groups with our members to understand this, safety means zero risk. As Lee said or Dr. von Eschenbach said, it's not what we say, it's what people hear. And in the course of a clinical visit, trying to communicate what that means, that in fact safety means acceptable risk given the likelihood of benefit for a patient or for a population of patients within the context of available alternatives. That's a 15-minute conversation just for starters. We need much better and more effective ways, and I think this is a very fertile area for research, of communicating risk and also communicating uncertainty. One of the biggest challenges I think for clinicians involved in day-to-day practice is communicating the level of uncertainty that exists about any intervention and not just prescription drugs and the likelihood of benefit.

The second challenge is the incredible diversity of practice settings. I work in an organization in an integrated delivery system. I'm one of 6,100 physicians in a collocated practice with

incredible support of fully automated electronic records and 60 years of longitudinal data on a defined population. I was stunned to hear Dr. Shiff say that in the most-sophisticated clinical environment in the world, Boston, he doesn't know all the drugs his patients are taking, and that's in Boston. Seventy percent of the care in this country is delivered in doctors' offices with three or fewer physicians. The last estimate I saw of computer physician order entry of ambulatory or outpatient prescriptions was we were approaching 25 percent.

MS. : That sounds high.

MS. LEVINE: That sounds high? I'm an optimist --the diversity of settings, the size, the infrastructure, and level of support to enable physicians to translate in a meaningful way information they're getting, and certainly connected to that is level of technology enablement of practices. The vast majority of physicians have electronic billing systems in place. Again, beyond

that in terms of electronic health records, it's quite sparse.

Finally, the fourth issue and I think growing issue is a need to enhance the signal-to-noise ratio that physicians get physicians get in terms of safety information. The significance of findings to their clinical practice, first of all, several people have said that physicians aren't trained in epidemiology, they're not trained to make independent judgments about that, at least they weren't. Medical school curriculum may be changing.

Now I'm going to transition a bit to some critical priorities I think from the perspective of practicing clinicians for the FDA. As we stand on the verge hopefully of rapidly increasing use of computerized order entry systems, I think it's critical for the FDA to partner with the vendors who are producing databases that are populating these CPOE systems. We currently have a Tower of Babel, different vendors use different risk standards, they use different drug-drug interaction methods, and it's

not uncommon for a clinician who is using a computerized order entry system to see one level of risk assigned to a drug or drug-drug interaction and the pharmacist who's dispensing the drug sees another. So what the patient hears from the doctor in an ideal situation may differ a lot from what the pharmacist says when they get to the pharmacy. Standardizing the format and a commitment from all vendors who are developing these drug databases would be enormously beneficial.

There are lots of opportunities for standardization as we've heard all day today. Safety alerts. Standardizing safety alerts, I'm sure this will create shivers down your spine, Janet, but complete, concise, and consistently formatted safety alerts, so that clinicians when they see a safety alert, they always know where to look for what information. It would be very helpful if there were the inclusion of severity frequency and clinical importance of the safety alert. I will tell you that I've had the privilege of practicing in an

organization where all this stuff gets formatted for us with a consistent template and interpretation in fact of the significance of the alert, for which physicians, and applicable to which patients. It's an incredible luxury, and our docs have just gotten used to practicing in that environment and would be devastated without it.

Another issue is the alphabet soup of categories of risk information and how they differ. Black box warnings. Some, great, some not terribly helpful. One of the chloroquine drugs has a black box warning that says, "Complete familiarity with the complete content of the package insert is suggested." Again, it's not terribly helpful. This isn't a criticism. This is an opportunity for the future. We're all moving toward a common language. The difference between contraindications, side effects, and black box warnings and what does that mean in clinical practice. And I think an opportunity to relook at the issue of push communication versus pull communication. Again the noise of early

communications which I think have been done with all good intent around we've heard some information and we're looking into it, creating noise when there in fact is a significant safety alert that is coming out and appearing on people's desktops either in paper format or in electronic format, and whether there's an opportunity for an FDA website designed for busy clinicians that in fact could be a place people went to to look for early communications, something that doesn't yet rise to the level of a push communication that says clinician take notice of this. And when should a push communication happen? My own perspective is when it affects something you're going to do. It isn't about general information or background knowledge. It will change something or potentially change something if you pay attention to it, something you do in the office.

I think I'm running out of time, but it may be worth considering as Mark said creating an advisory committee on communications both for citizen communication but also for clinician communication and

how to make this stuff cheap and easy, make it really easy to do the right thing I think is the goal of all of this. I was going to talk about the risk maps but I think I will stop there. Actually, can I just take one minute?

MR. MCCLELLAN: You have one more minute.

MS. LEVINE: Thank you. This is from the perspective of working in a system that is a data owner. As I said, we have 60 years of longitudinal data that goes back on a population, we now are caring for third- and fourth-generation Kaiser members in Northern California, and now a fully automated electronic health record. There are IRB issues in relationship to data queries. There are also institutional issues. And every research proposal we look at has both an IRB review but also a review for institutional impact. The notion of an open platform available to all researchers I think creates a whole slew of problems that could get in the way of this critical work on pharmacovigilance. And also again I think just representing the researchers who are

connected to the Kaiser Permanente program, their great hopes and enthusiasm for participating in the Sentinel Initiative and the concerns, that their access to research and participation in research not be precluded by the way this gets set up. Thanks.

MR. MCCLELLAN: Thank you very much. We have time for a few questions. Are there any questions on some of the many topics that this panel has brought up?

MR. : I am Sharif -- I just finished my first year of medical school. I wanted to comment on one of the things that you said about developing clinical curriculums. I am experiencing this first-hand and I know for a fact that clinical epidemiology is being emphasized in medical curriculums across the country and there's going to be a new generation of clinicians who are definitely adept at interpreting clinical data. Given this, I'm wondering what that indicates to you in terms of the ability to control the many levels of communication that will be involved especially since we're going to

have situations where you have unsubstantiated but the potential for type 2 statistical errors and you have findings and signals that aren't yet substantiated by hypothesis-based research, but you're going to have clinicians who are going to find out for themselves who are going to be researching this themselves going on the FDA website and especially if they prescribe these new medications themselves on a routine basis they're going to take the initiative to find out. So I'm wondering if you can comment on what you see as a developing capacity to control communications given that there's going to be this new generation of physicians who are definitely adept at interpreting it on their own.

MS. : I would never suggest controlling communication, and we do have 600,000 physicians. We have to deal with the population out there we've got. My issue is not preventing access either to consumers or physicians about information, but the issue of context that Mark spoke about is really important and the issue of making it really

clear the level of certainty that exists for those who can't and don't have the time quite honestly to go into the primacy sources, the level of certainty that exists and how potentially it should impact the way they think about clinical conditions. And I think the Vioxx story was a great example. We've lived with drugs that have created cardiac risks for decades in terms of chemotherapeutic agents. I think the outrage or the anger that resulted from the Vioxx story was that it was a trivial drug from a clinical perspective that created increased risk of a serious problem. So this issue of understanding the risk of the drug and be confident that the benefit it potentially offers to an individual or population is congruent with meaning at least better than the potential for risk.

MS. ZUCKERMAN: I'm Diana Zuckerman from the National Research Center for -- I wanted you to congratulate you for this whole day, but I also wanted to emphasize what you just said. It's the context. When you're talking about safety it's not just the benefits and the context of the risks but also as you

said, Sharon, compared to other alternatives and I think there hasn't been that much said about that. And when we're talking about research and looking at risks and benefits, that those alternatives are really important both in terms of the chronically ill patient who may have no alternatives, but also Vioxx is a perfect example of where patients have lots of alternatives or at least many patients have lots of alternatives that are safer and to make sure that when we're looking at the data people look at that whole context.

MR. MCCLELLAN: Thank you. Are there any further comments?

MS. : I think that last point gets into the trust in that consumers, even though we at our website and Consumers Union and other groups are trying to develop consumer-friendly comparative effectiveness information, I think that that trust really starts with the physician and we make the assumption that our physician understands the therapeutic options and the nontherapeutic options.

But we as consumers do need to be a little more proactive about asking how they arrived at that if we're familiar with the other choices, but I think it gets back to the trust.

MS. : Speaking from the physician perspective, trust is equally important, and I think one of the incredible potentially most powerful outcomes of the Sentinel Initiative is that this will be information from a credible, independent, largely trusted agency. As Janet said, the management of, not just management, but avoidance of conflict of interest in the way this is set up will go a long way to making this the primary source of information that people look to to understand what it is they should be doing.

MR. : I would add to my plug of having some sort of committee structure where you have patients and consumers involved to again not interfere in the science or interfere in the governance, but to be there to provide credibility and context in the communication because these issues are going to find they way into the laps and conversations at breakfast

tables of real people and if it's not provided through the context of real people, we're going to have distrust in terms of the information and I think that's a critical piece to make this operationally successful in terms of public health.

In this day and age where the only TV we watch is reality TV. The reality is people are looking for communications for other real people. They're on blogs. They're watching reality TV. We've got to provide that same context in terms of public health.

MR. : Mark, it's Glen -- again. If I've assimilated what we've talked about this morning, we said we wanted a system that has all the data in it that isn't missing some systematic piece so that we don't have a bias which means we need the health care providers and the pharmaceutical industry to be able to provide the data. We want to have the trust of the public which means we don't want to filter communication or we don't want to mislead anyone by communicating too soon, and we need to set

up a system that has a research objective that's open to everyone to be able to work with, all at the same time meeting the public needs. That's a lot to put together. Some day we're going to do that, but my guess is we're going to have to make tradeoffs to get started. Who and how will we make the tradeoffs necessary to get version 1.0 up and running, integrating all the great perspectives that have been brought to the table today? That's a question for you, Mark, by the way.

MR. MCCLELLAN: If you all want to answer, that's fine, too, but that's a nice transition to the wrap-up for this session. Before I do that, I want to recognize more speaker at the back.

MR. : I couldn't let the moment pass because I really feel compelled to emphasize the importance of what's being discussed as it relates to trust and communications. From that perspective I want to underscore what was said at the very beginning of this session this morning.

Part of that establishment of trust with regard to a patient and a physician, and I'll speak from that perspective as a physician, is that that patient has to always know that what you're doing is for them, that they are the end and not the means to an end, either the means to be making my payment on my next BMW or writing my next paper so I can become famous, that what we're about is doing something that's for them. This initiative has to be always framed in that context. I said this morning FDA is not doing this because Congress told us do, and someone else said we're doing this because this is a public-health issue in a public-health context. So whether we're talking about the science or whether we're talking about the research or whether we're talking about gaining new knowledge for a variety of purposes, et cetera, FDA will always be approaching this from the perspective that this is being done to serve patients, to be able to make certain that their health is being protected and promoted by the information that's being gleaned and gained from this

initiative, and I just didn't want to let that moment pass without underscoring that message. Thank you.

MR. MCCLELLAN: That's very much. That's a great comment to wrap up on. With that goal in mind, I think many of you or all of you have heard today -- the word transformation has been said a number of times, and transformations in the patient's interest is something that we hear about a lot, talk about a lot. Hopefully what's come out of this discussion today is that there is potentially a real path to get there, but also to Glen's point that these kinds of changes don't come easily. They don't come without obstacles and they don't come without many barriers and challenges that need to be overcome. Our main purpose in holding this meeting today was to try to get as many of those out on the surface and up for discussion as possible and I think if we've had a meeting where the discussions range from concepts of distributed data networks, all the way over to complex data analysis and methods, and on to 20th century art and reality TV, I think we've done a pretty good job

of raising a number of issues. But also hopefully creating the kind of -- I think Janet called it a social network, not a social network around a reality TV show or Facebook or something like that, but a social network around the next generation and what could be a transformation in how evidence is developed and used to improve not just the safety of drugs but improve the safe and effective use of medical treatments.

This has been a start to that process. It's one element in a larger process that FDA is conducting now as they really try to take advantage of this unique set of opportunities at this time in our nation's history. It will not be the last step. We intend at Brookings to continue to build on the efforts today. We will have some further meetings and some papers on some of the topics discussed today, this kind of framework for how post-market evidence can be better developed, some of the governance and infrastructure issues, the new data and methods, the legal and privacy issues, communications issues, and

impacting patients' lives positively, having a positive impact on practice, we aren't going to be only ones doing this. And you've heard from a lot of other groups that will be continuing activities as well, but I do think that by working together we can make sure that we take advantage of these opportunities as effectively as possible.

With that in mind, I want to thank you for your input today and also highlight that we will be seeking more input in these further activities, and just end up with a special thanks to all of our panelists as well as the people on the staff at the Engelberg Center that made this possible. That starts with Christina Lowell. I'm sure you've recognized that she's I think going to have her baby tomorrow or something. I know you've heard this joke a dozen times, but I think the middle name is going to be Sentinel or something like that. Also Justin Short, Theresa Wheatley, Marisa Morrison, Jenny Lilgeberg (ph), Emily Wheeler who did a tremendous amount of logistical work and support work for this meeting,

Gary Carr who helped with the press, Larry Cochut (ph) who does everything, and everyone who hosted us here at the University Club. But most of all, thanks to all of you. There clearly is a strong level of commitment to doing a fundamentally better job with these opportunities we have to improve post-market evidence and I hope that we'll continue to be able to work together to make that happen for the benefit of patients. Thank you all very much.

* * * * *

CERTIFICATE OF NOTARY PUBLIC

I, Carleton J. Anderson, III do hereby certify that the forgoing electronic file when originally transmitted was reduced to text at my direction; that said transcript is a true record of the proceedings therein referenced; that I am neither counsel for, related to, nor employed by any of the parties to the action in which these proceedings were taken; and, furthermore, that I am neither a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

/s/Carleton J. Anderson, III

Notary Public # 351998
in and for the
Commonwealth of Virginia
My Commission Expires:
November 30, 2008