

The Food and Drug Administration and eHealth Foundation
In cooperation with the Brookings Institute
Sentinel Initiative: Structure, Function and Scope
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Welcome, Introductions and Meeting

Janet Woodcock: Good morning. Thanks. Those in the back, there are seats along the sides of this table. We wanted to have a sort of as intimate as possible discussion with so many people so we have the seats surrounding the panelists. Welcome to the public workshop on the FDA Sentinel Network. I'm Janet Woodcock, and I'm the director of the Center for Drugs at FDA and I'm also the senior executive sponsor at FDA for the Sentinel Project. We really are happy to be having this first public meeting about the Sentinel Network and the Sentinel Project that we are doing.

Congress, in the fall of 2007, passed the FDA Amendment Act and in there, they mandated that FDA set up an active surveillance system for drugs utilizing electronic data from healthcare. FDA has taken this on in our Sentinel Initiative as we call it, which is the project to build this new active surveillance system, which we called the Sentinel Network, and we are going to do this for all FDA-regulated products that might have healthcare data pertaining to them not just for drugs.

There are many sources of electronic health data in the United States as most of you know and the number is growing every year so this is a time of opportunity. Now, FDA has long utilized claims databases to investigate safety questions about products but this has always been on a one-off basis. We have worked with one particular healthcare system to identify the data performed in an investigation and analysis and then looked at the results.

The goal now is to create a linked sustainable network so this can be done either in real-time or in very short to real-time and we can continuously evaluate questions about medical product safety in our healthcare system in United States. Now, doing this is actually -- we have had a whole series of meetings with various stakeholders, specific communities such as those who actually have these types of data and providers and so forth. And we have learned that this is probably technologically feasible to do what I just said, and there have been some attempts and experiments as you will hear later in the day to try this out.

But doing this - setting up a long-term sustainable network - raises many questions and these are questions of great public interest. These are questions about governance of such a network, about privacy, about the data standards that we would use, about data handling, public availability of results

and so forth and so on. FDA is really committed to an open public process as we grapple with these issues, and we actually construct version 1 of the Sentinel Network. We recognized this is going to be an ongoing project and like most of this sort of IT type of applications, we will have version 1 and we are aiming for a long-term version that will be probably much more functional but our goal is to get version 1 up and running.

Today, we will raise many of the issues that are of public interest in constructing such a network and we are hoping for vigorous participation from each one of you. And we have established breakout sessions that will be in smaller venues so, hopefully, everyone can speak up because we really do need to hear from everyone who has an interest in this as we go forward. The design of the workshop engages a panel of experts who will lead discussions on specific topics, and that is who is sitting around this table. So I think I would like to have each expert introduce him or herself and we will start at the end of the table there, so if you could start and we will go away around. Thank you.

Cherif Benattia: I'm Cherif Benattia. I'm the head of the Pharmacovigilance & Public Health at Vertex in Cambridge, Massachusetts. I have been working in risk management in the

city for some years and I teach all these topics in the U.S. and outside.

Ed Pattishall: My name is Ed Pattishall. I am the VP of Clinical Safety and Pharmacovigilance at GlaxoSmith Kline. I am leading a project on how to look at multiple disparate observational databases called SafetyWorks.

Kristen Rosati: I'm Kristen Rosati. I'm a partner at Coppersmith Gordon Schermer & Brockelman in Phoenix and also general counsel to eHealth Initiative and was involved in eHealth Initiative's drug safety collaboration looking at all the legal issues involved for the participants in pharmacovigilance.

Scott Smith: Good morning. I'm Scott Smith with the Agency for Healthcare Research & Quality, where I'm with the Center for Outcomes and Evidence. We have two active distributive network projects that I'm a project officer for.

Tom Gross: Good morning. I'm Tom Gross. I'm the director of the Division of Postmarket Surveillance at the Center for Devices and Radiological Health, and we are very interested in this initiative from a device safety perspective.

Carol Diamond: Good morning. I'm Carol Diamond. I head up the Health Program at the Markle Foundation. I also chair our public-private collaborative called Connecting for Health, and we have been focused on issues of information-sharing, the

role of the consumer and the networks for some time, so I look forward to the discussion.

Barbara Evans: Hello. My name is Barbara Evans. I'm a law professor and I'm co-director of the Health Law and Policy Institute at the University of Houston.

Deven McGraw: I'm Deven McGraw. I'm director of the Health Privacy Project at the Center for Democracy and Technology.

Rick Kuntz: My name is Rick Kuntz. I'm the president of Neuromodulation at Medtronic, and I previously was the chief scientific officer at the Harvard Clinical Research Institute.

Marcus Wilson: Good morning. I'm Marcus Wilson. I'm the president of Healthcore. Healthcore is Wellpoint's health outcome research subsidiary. We utilize the data resources and data environment from Wellpoint to generate medical evidence on safety, effectiveness and quality of care.

Sebastian Schneeweiss: I'm Sebastian Schneeweiss. I'm an associate professor for medicine and epidemiology at Harvard Medical School and I work in the Division of pharmacoepidemiology on drug safety issues and methods development.

Vik Kheterpal: Hi. I'm Vik Kheterpal. I'm principal and chief medical officer at CareEvolution. We are a health IT infrastructure company for connectivity, and we have been

working with a couple of states in generating linked datasets while preserving privacy so that you could track outcomes over a longitudinal basis.

Shawn Murphy: Hi. I'm Shawn Murphy. I'm medical director of Research Computing and Pharmacovigilance at Partners Healthcare in Boston, and worked extensively in the eHealthcare Initiative. We are one of the communities along with Regenstrief used to prove many interesting concepts of how to use pharmacovigilance data in this endeavor.

Melissa Robb: Hi. I'm Melissa Robb. I work at FDA's Office of Critical Path Programs, and I'm the project director for the Sentinel Initiative.

Rachel Behrman: Hi. I'm Rachel Behrman also with FDA's Office of Critical Path Programs and the executive sponsor of Sentinel.

Janet Marchibroda: Good morning. I'm Janet Marchibroda. I'm the chief executive officer of the eHealth Initiative and its foundation, and delighted to be supporting the FDA with this work.

Mark McClellan: Good morning. I'm Mark McClellan. I'm the director of the Engelberg Center for Health Care Reform at the Brookings Institution. I'm the chairman of the board for the Reagan-Udall Foundation. It is a pleasure to be here.

Richard Platt: I'm Richard Platt. I'm a physician epidemiologist at Harvard Medical School. Until recently, I chaired the FDA's Drug Safety and Risk Management Advisory Committee.

Marcy Wilder: I'm Marcy Wilder at the law firm of Hogan & Hartson and a former deputy general counsel of the Department of Health and Human Services.

Joseph Selby: Hello. I'm Joe Selby. I'm a physician and the director of research for Kaiser Permanente in Northern California and the principal investigator of one of the FDA's four population-based risk assessment contracts.

Alec Walker: Alec Walker, WHISCON and Harvard. I developed and oversaw the implementation of an early system for looking at all possible outcomes in all new drugs at i3 Drug Safety.

Fran Cunningham: I'm Fran Cunningham, Director for the Center of Medication Safety at the Department of Veterans Affairs, and I'm responsible for primarily most of the pharmacovigilance and medication safety efforts at VA.

Michael Berkery: I'm Mike Berkery, Chief Technology Officer of the American Medical Association and responsible for our health information technology initiatives.

Jesse Goodman: I'm Jesse Goodman, Director of the Center for Biologics Evaluation and Research. We oversee vaccines,

blood, a number of novel therapies, and our Office of Vital Statistics and Epidemiology has done very promising work with colleagues at CMS, CDC, et cetera, including near real-time monitoring of vaccine adverse events. I'm also an infectious disease physician.

Zoe Baird: Thank you. Hi. I'm Zoe Baird, president of the Markle Foundation. As Carol said, we work on accelerating the use of information and information technology to improve healthcare.

Garry Neil: I'm Garry Neil. I'm head of Corporate Science and Technology at Johnson & Johnson, and I'm a member of the board at the Reagan-Udall Foundation.

Jeffrey Kelman: I'm Jeff Kelman. I'm the chief medical officer at the Center for Drug Plan Health Plan Choices at CMS. We run the Part D Drug Program.

Arnold Chan: Good morning. I'm Arnold Chan, an epidemiologist with i3 Drug Safety and Harvard School of Public Health. I do drug safety research and also engage in methodology development for medical product safety surveillance.

Don Beers: Good morning. I'm Don Beers, an attorney in the Office of Chief Counsel of the FDA.

Trinka Coster: I'm Trinka Coster, a physician at Department of Army, Director for the Office of the Surgeon

General's Pharmacovigilance Center in Silver Spring. We are involved in drug safety passive and directive and eventually, active surveillance.

Josh Benner: Good morning. I'm Josh Benner. I'm a pharmacoepidemiologist at the Engelberg Center for Health Care Reform at Brookings.

Current Status of Sentinel

Janet Woodcock: All right. Thank you very much. As you can see, we have a distinguished group of panelists who represent a very broad range, I think, of societal perspectives and, hopefully, stakeholder perspectives on this issue so we really look forward to hearing from all of them during this day.

The next step, I would like to brief you all on the current status of Sentinel, where we are, and also talk a little bit about the objectives for the meeting today a little bit further. I'm going to go through first an update of where we are, what FDA is doing on our project to make Sentinel a reality and the first part of the meeting then is to bring everyone up to date. We will have a question and answer discussion after this presentation so we can make sure we are starting the day on the same page and then the meeting objectives include getting a broad discussion among all the stakeholders on a variety of topics; particularly, we are going

to discuss governance models and how we would apply them to Sentinel because of course, this data that we will receive from doing active surveillance, I think, has to be seen as a public good. It is something that not just the FDA probably but many parties could benefit from - the use of these data and the understanding of these data.

And so the question is, how do we set this up, this structure up in a way that protects privacy and protects the participants but at the same time allows as much openness of data as possible? And then we also would like to hear from all the stakeholders about the best way as we actually put this together and launch version 1.0, how we can keep all the stakeholders involved in this initiative.

So first, let us go through where we are right now. As I said, the FDA Amendments Act was really the genesis of this project. Although the FDA had been contemplating this for some time but it was really jump-started by section 905, which required FDA to collaborate with public, academic and private entities to develop methods to obtain access to disparate sources of data and validated methods to link and analyze safety data from multiple sources and of course, this is in the legal language kind of the statute, but over time we have really sort of refined what we think this might mean by talking

to all experts, including groups such as AHRQ and others who actually have done some projects such as this and eHealth.

And then we were required in this statute to have access to data from 25 million patients by July 1, 2010. From the government point of view, we are already in the 2009 fiscal year, so we are moving right along and we are going to have something up and running - some access by that time - and we intend to meet that deadline. And then access to data from 100 million patients by 2012 and of course, I think once we get this up and running, that is going to be the hardest step and then adding additional data sources may be fairly straightforward after that.

Now, the Amendments Act also established the Reagan-Udall Foundation, which is a private independent non-profit entity whose mission is to advance the mission of FDA in scientific modernization and so forth, accelerate innovation and particularly, enhance product safety. And so as Mark McClellan just said, he is the current chairman of the Board of the Reagan-Udall Foundation, and that is an entity under which FDA can form collaborations with outside entities and set up structures such as we are contemplating doing for the Sentinel Network.

Our initial vision of Sentinel is we would develop it as a nationwide, electronic safety monitoring system - and I think

everyone is clear on that, using electronic health data, but what we need to make clear to everyone is that our initial vision includes the fact that the data itself will remain with the original owners behind existing firewalls in general. So we are not intending to build a large database wherein primary data is aggregated within Sentinel.

What we are thinking about instead is a distributed network where the network actually sends queries out and gets results back. The owners of the data, whoever they might be, would usually run the queries under the idea that we have put forth so far. These queries - and this is one of the governance issues - they would be requested by FDA or they might be requested by other partners of the collaboration. And then, the data owners would run those queries within the safety of their own system and then send the results back to the network for analysis, and we would have to have strict privacy and security requirements for those data that they would stay primary data with the owners.

Now, what we think we need to set up a system that would enable FDA to partner with existing data owners such as insurance companies, such as healthcare systems that have electronic health records, such as practice collaborations that have electronic health records and so forth so that we could access those data sources. Also, we have the VA and we have

DoD here at the table; they have obviously data sources as well as CMS. Now, this new system which would strengthen FDA's ability to monitor postmarket performance of a product, but it would also strengthen the ability of all those partners to make sure because they will have a responsibility to their patients and it will strengthen their ability, and that is why we view this as a natural partnership because those other partners also have a stake in the safety of the population they are responsible for.

Also, it is important to know that we are considering this as augmenting FDA's repertoire of ways of monitoring safety, not replacing what we have. We have spontaneous reporting where the people out in healthcare send us reports through the various manufacturers - reports are sent to FDA. We are continuing to run that system and we plan to continue to run that system. We require postmarketing studies; we require registries. There are a wide variety of postmarket safety activities that are done by FDA. This would be another tool in the toolbox, although perhaps as the versions would grow, this would become one of the most powerful tools we would hope. But there is confusion that this would completely replace other functionalities that we have.

Also in this vein, let me just say that we are not seeing this partnership as replacing FDA's function in postmarket

surveillance. So as a result of queries that are run in this network, FDA may have to do its own investigations under its own authorities and that also would continue as it currently happens. So this would be another way that other healthcare systems as well as FDA can actually improve patient safety.

Now, the Sentinel Initiative has to be viewed, we think, as a long-term project that will be implemented in versions or stages and will necessarily evolve, and one of the reasons is that the quality of the data and hopefully the standardization of the data out there will improve over time. Right now, we know that it is somewhat of a cacophony and so, we are going to have to be very careful about how we design and run these queries because there are all sorts of different data out there.

So what we are trying to do now to move this forward is work on the how and the what for version 1.0. We hope we are creating a broad public forum for discussion of the issues related to developing and implementing the system. We want to do this completely out with the public, delineate the structure and functions that will lead to foundational documents for establishing the entity, so what we want to hear from you are what are the things that you are concerned about because as we are writing those documents that will establish this

partnership, we want to make sure those issues are taken into account and explicitly laid out somewhere.

Develop a cohesive structure for shared learning from ongoing related activities and you are going to hear about some of the projects that are going on, but as you just heard from the experts around the table, there is a lot of work going on in a lot of sectors that can contribute to the thinking that goes into Sentinel; we need to make sure that it is folded in. Identify steps necessary to ensure strict privacy and security safeguards, and we have a number of experts and lawyers and other privacy experts here at the table to help us with that. And then, evaluate and establish risk communication principles.

One of the concerns everyone has about this is we have never done this before as a society and as we run these analyses, at first, we really will not know what they mean and so we are going to have to guard against this as far as any premature announcements or incorrect conclusions and so forth. We are going to have to have methodologic rigor and connect that to our risk communication activities. And the new system must provide for better safety capacity for our nation but acknowledge FDA's regulatory role. So we need to make sure this partnership and this data serve FDA and others but also recognize that FDA has a separate regulatory role that we will continue to operate.

Now, governance we have learned can mean many things to many people. For the purposes of this meeting, governance defines the responsibilities for developing and implementing policies and procedures, for administering certain aspects of the initiative - the scientific infrastructure, the operations, and all the policies and so forth. And designing and maintaining identified capabilities and needed function such as scientific methods, data infrastructure, communications and privacy.

I have been involved in putting together a number of collaborations similar to this in different spheres, and I can tell you all of course, all of these things take a long time and must be done extremely carefully to make sure that all the interests of all the different parties are acknowledged and everything is clearly laid out, and we intend to do that; that is going to be the work of the next six months for us.

Now, another thing we want to talk about is learning from the multiple related activities that are now underway. Fortunately, we are not doing this blind. A lot of groups, both in the private sector and in government, have been doing activities that might be considered almost pilot activities; they have been doing this, they have been trying it and this includes the VA and DoD. FDA is working with CMS to look at their part D data and the other linked data and to see how that

can be analyzed. For the private sector activities, we are acting in an advisory role so that we can learn from what the private sector is doing.

So here is a long list of organizations and initiatives that pertain to what is going on with Sentinel: AHRQ'S effective Healthcare Program, Brookings, and Dr. McClellan here also has been engaging in this and have been having forums on postmarketing evidence, the Center for Biomedical Innovation at MIT has been doing work on this, the CERTs, which is through AHRQ and with FDA, the HMO Research Network, eHI - as I have already mentioned - and their drug safety collaboration; they have been running pilots - the International Society for Pharmacoepidemiology, the OMOP Initiative, which is through the Foundation for NIH, which is explicitly looking at methodologic research, researching the methods to do these types of queries, and then as we have heard around the table, a number of the healthcare systems and entities themselves are doing evaluations within their own systems and that is also germane. So that was a long list, but this is just to acknowledge these efforts and also say we have been in contact with people working on this.

In addition, recently, FDA has led a number of contracts to help us in getting this whole project together: from Harvard Pilgrim, we have defining and evaluating possible database

models; Group Health Cooperative Center, evaluation of existing methods for safety, signal identification for the Sentinel Initiative, evaluation of timeliness of medical uptake for surveillance and healthcare databases; IMS Government Solutions, evaluation of potential data sources for the Sentinel Initiative - this is an important one, a contract let to Booz Allen Hamilton.

In addition, for blood and tissues in the biologic sphere - that is a specialized area - we have a contract to look at data sources and Pragmatic Data is doing that contract. Evaluation of potential data sources for national network of orthopedic device implant registries because apparently, these are all separate and that is by Outcome Sciences. Engagement of patients, consumers, and healthcare professionals in the Sentinel Initiative - the eHealth Initiative has been contracted to assist us with that. We really need to make sure we reach out to all the involved stakeholders. And then, developing a governance and operation structure for the Sentinel Initiative - this would be the set of defining documents that would describe how the partnership would work, and eHealth is also going to be working on that.

So with all this going on, one of the concerns is to make sure that all the involved stakeholders have a transparent inclusive process they can participate in to know what is

happening, and they can also gain input on the many components related to Sentinel, both the process as well as all these documents and the actual science that we are going to be doing in the Sentinel Initiative.

So my last final slide is Next Steps. The outcome from this meeting will define the initial foundational structure of Sentinel; although, I can assure you that the devil is going to be in the details, and as we write these documents, many questions will arise. There will be many branching decision points and that is why we need to make sure we have an inclusive process, to make sure we continue to get feedback from everyone.

We hope in the next six months to have draft documents; that does not mean we are going to put them on the FDA website and show them to everybody, but we hope to have some kind of structure and then we would commit to certainly having additional meetings and public forums so that people can understand the initial direction we have planned on. So we are going to let more contracts to hopefully move this entire effort along and then continue to have this process.

So thank you very much for listening to this background. That is how we got to where we are today. So what we are going to do now is have a question and answer session, briefly. First, I would like to ask any of the panelists to react to

what has just been said or add anything. I certainly could not put everything in there. Mark, do you have something you would like to -- somebody has to break the ice here.

Question and Answer Session

Deven McGraw: Janet?

Janet Woodcock: Yes? Great.

Deven McGraw: Actually, a couple of them from your slides. With respect to the effort that you are doing to evaluate database models, can you provide me with a little more detail because you said in the beginning that the owners are going to run the queries and you are not, so I was under the impression that you were not creating a database that FDA or the Sentinel Initiative would run, so what is that group doing?

Janet Woodcock: Very fortunately, we have Dr. Platt here who can address this point with greater specificity.

Richard Platt: The first version is almost certainly going to involve some translation of the native data systems into some kind of a standard format that would stay behind the firewalls and be owned by them so that a single query could be distributed and run. When everything goes well, you push the button and the results spill out. That would be the notion; it is to develop a common data model.

Janet Woodcock: Yes, so for the benefit of everyone in the room, this is almost like the United Nations or something

where we want everyone to come together but they all speak a different language and we do not want to force them to all speak the same language but we need to put behind their firewall a translator, so we translate the queries into their language and then we translate the results. I mean I know this is very primitive, I'm sorry, but we kind of translate the results back into something that is when it is transmitted, everybody else can understand. So that is what we are talking about in the model. We have to understand how the data are configured in each of these systems that might link up. Are there other questions? Yes?

Cherif Benattia: [Inaudible] overview. This is a very interesting initiative, still a lot of challenges.

I would like to know if you are seeing one big database or different databases. And if there is one large database, will this be kind of the reference database or no? Meaning, if you have data collected in the RAMs or risk map from all the databases, will this large database serve as a reference or no and if there is conflict, where would we go? So a different question -- the main question is, will this be a large database and will this be a reference database for all other databases?

Janet Woodcock: No, I do not think -- what we are starting with version 1.0 is simply to enroll a number of volunteers who will be willing to have this translation service

be put behind their firewall and participate in these distributed queries and then they would send results back. Does that answer your question or not? That does not address your question --

Cherif Benattia: Not really, in the sense, how will we use this compared to data that, for example, the industry will bring from other databases and if there is a conflict?

Janet Woodcock: From other data compared to other data --

Cherif Benattia: Yes.

Janet Woodcock: Well, I think this is one of the central issues that we are going to have: How congruent are the results going to be when you do queries in various systems or evaluations in various data systems behind different firewalls? The FDA has the ability, and that is what I said earlier, we can go in a public health role and perform a more in-depth investigation if there are a lot of disparities of the results that come out of different systems. That can be investigated further.

Richard, do you have --

Richard Platt: I think that is the right answer. You know we are likely to be in an interesting position of going from being very data poor and hoping to find one data system in which we might get an answer to having several data systems and then realizing that there is a lot of variation between data sources. So I think there is going to be a substantial amount

of work in trying to do that reconciliation. Frankly, I think that is a good thing that we will start to understand in a much more detailed way than we have ever had an opportunity to do how safe drugs are.

Janet Woodcock: Also, this raises a point I did not put in my slide which is, I believe our mutual function that we put together in Sentinel, we will need to have a strong research component and that may not have to reside in the partnership but it will need to be supported by the partnership because by research, I mean methodologic research, because I do not think we know the answers to some of these questions but there are empirical ways we can research them and find out. I believe if we find disparities amongst different queries that are run in different databases, that is a scientific opportunity to understand how the data structure influences the results that you get.

Cherif Benattia: Okay, thank you. I have other questions but I will send them to you by email because they are just very detailed.

Janet Woodcock: Absolutely. Yes, Jesse?

Jesse Goodman: I would just like to mention a couple of issues that I think would be of interest in people's opinion. One is from the perspective of somebody engaged in trying to use these kinds of data, I think, ideally, FDA would have

unfettered access to anything in this system. So when I hear about queries and studies, my view would be we need to transition from that kind of one-off thing to just having access, and one concern is that if there are -- obviously, the questions would need to be feasible and the quality of data would need to support those or the studies should not be done. But I am just raising the question that if there were some things that could be done and some that could not, it could raise questions about how those choices were made when they should be driven by our public health responsibilities.

And then, the other issue I was going to ask about is, can we or should we build this so that it goes beyond queries but that the instruments allow us to do, in fact, surveillance recognizing the limitations? In other words, the kind of near real-time work that again as a regulatory agency we need to do, again recognizing its limitations.

Janet Woodcock: Comments on that? I think of course, it may be possible to do some real-time surveillance right away that we might be able to design that in. That is going to depend on just how we build things.

Richard Platt: I think the term query is sort of shorthand for executing a program that runs behind the firewalls, and so I take it to include surveillance as one of the technicalities [sounds like].

Janet Woodcock: Yeah.

Male Voice: Also, in terms of following up on questions about data, the kinds of reasons that FDA might want to have full access is, say, to the individual data, many of the systems that have been used to do these kinds of activities before, including some that Rich has been involved with for vaccine surveillance and that you are familiar with, have what is called the traceback capabilities. They do not need to pool all the data but if there is a question or need for confirmation about the details of a specific case, there is a mechanism working with the data owner to make that happen.

Janet Woodcock: Are there other comments on that? The people in the back of the room, there are some seats over here if you do not want to keep standing. This is a good time you can sit down if you would like to have a seat. Are there other comments on that?

I think one of the questions about governance that we are going to have to address is who gets to do these queries? That is a major question. Obviously, FDA would get to do these queries. Who else gets to do these queries? The partners should probably be able to -- they can run queries now in their own systems. Should they not be able to use the whole system if they have a question that is pertinent to their healthcare system? So those are some of the things that we are going to

have to work our way through as we develop the governance. Are there other comments on that or other questions? Yes?

Suda: Thank you, Janet. Good morning, everybody. My name is Suda [phonetic] and I'm representing Magnata Inc. here. I have a question. First of all, thank you, we are very excited to be here. Our core product is codified electronic medical records system along with chronic disease management, and we use standards SNOMED, CCR, CPT, ICD-9 - the whole gamut. We are very interested in participating in this group. The initial foundation structure of the Sentinel, we want to contribute in creating the draft documents for establishing partnerships, talk about the mode of communications. Is it XML? How do we communicate? How do we share data? What do we give? What do we take? Where is what? So we want to be in it completely. Who do I contact? How do I begin? Where do I start?

Janet Woodcock: Yes. Well, for all of you, Melissa Robb is the project director at FDA for the Sentinel Initiative so she will be the person to contact. Thank you. I think one more question and we have to move on. Yes?

Arnold Kuzmack: My name is Arnold Kuzmack, an FDA patient representative. One of the concerns that I have with all of this is how accurate is this data? It is being put in by people whose main goal -- for example, the insurance database's

main goal is to get paid - then the scientific accuracy of the input is not particularly something they are concerned about. So I'm wondering whether there has been any work done to sample this data and sort of see how accurate it is for the purposes that we are talking about here.

A related question is if FDA gets some of this data in a query then it will be subject to the Freedom of Information Act. I wonder how you all have grappled with that little problem.

Janet Woodcock: Thank you. Well the answer to the second, what about FOIA or other query, that has to do with the governance. When we say something is still under investigation versus we have arrived at a conclusion either FDA with a partnership or whatever, we will deal with that in the document, so we do have to deal with that.

The first question, what about the accuracy of claims data and other data, there is big research literature on this. You are right; it is not very accurate so that is one of the methodologic issues we have to deal with as we go through this. Somebody want to comment? Yes?

Male Voice: Janet, I just like to say I think it is difficult to make a blanket statement about the accuracy of claims data. There is no doubt if you have a hip fracture in claims data that you do not need to check it. On the other

hand, if you have a hospitalization for congestive heart failure, it is almost surely not a good measure of congestive heart failure. So there is a range and people have been developing algorithms and there is not a single answer.

Janet Woodcock: Yes. So this is something again that is a matter of research and for vigilance. We recognize the data are not very accurate in some cases; not a good surrogate for what actually happened to the person. So thank you.

Arnold Kuzmack: Thank you.

Janet Woodcock: Okay, now, I think we will move on. I'm going to turn the microphone over to Dr. McClellan who is going to talk about the plan for the workshop. Mark?

Workshop Plan

Mark McClellan: Okay, thanks, Janet. This is moving from some of these big ideas and questions that you have just been talking about to the mechanics of the day and how we are going to make progress today on answering them. I would like to start by thanking all of you for coming. It is great to have such a big turnout. I would say though that this is not a standing room only meeting so again, there are plenty of seats on the sides for anybody who is tired of exercising their legs or has decided that they really do want to stay for the rest of the day. But this is also hopefully a little bit informal. This is a workshop where it is going to have a lot of back and

forth discussion. If you need to get up and walk around or walk out, that is fine as well.

Today's discussion is going to benefit from the large and diverse group of participants that you all comprise. We have here today senior FDA leadership, leaders from other government agencies, academic researchers, private sector experts, consumer and patient organization leaders, industry representatives, people from health plans, healthcare providers and many others. All of these perspectives are very important to the success of the Sentinel Initiative and your participation in this effort is very important to getting to the implementation of a Sentinel Initiative that is technically feasible and can work effectively.

As you heard from Janet, because your role is so important, not just for ideas but for the actual collaboration that is going to be required to make the Sentinel Network work, FDA is committed to developing Sentinel through a transparent and inclusive process. The agency, I think, needs active participation from a broad range of public and private perspective. So today is an important opportunity to exchange ideas about the structure, the function, the scope of the Sentinel System and to keep bringing it closer to effective implementation.

This discussion is going to build on a range of previous public forums and thoughtful ideas. Janet mentioned a number of these. At the Engelberg Center at Brookings, we have had the privilege of hosting some of the public forums on postmarket evidence. In one back in June, which is available on our website at brookings.edu; there was a diverse group of stakeholders who shared perspectives on Sentinel. What emerged from that meeting from some of these other discussions was a framework for some key issues to consider and the design and the implementation of the initiative. These, I'm going to go through briefly for a little bit more context setting before we get going in the details of the meeting today.

One of these big areas, as you have already heard, is governance and infrastructure. The FDA Amendments Act stipulated that the postmarket risk identification and analysis system to be developed in coordination would be done with public input, academic input, with the role of private sector entities participating, but more work is needed on exactly how to do this. For example, policies regarding access to the Sentinel Network by other researchers as we have heard about already; funding for the system, particularly the private contributions into it; management of the scientific operations and its infrastructure all still need to be determined. And these are all going to be a part of today's discussions.

Ideas about governance and infrastructure cannot be considered in a vacuum but in the context of the goals of the network, which brings me to the next slide, which is one key part of the network is bringing the data and scientific methods together to augment our ability to develop evidence on medical treatments that are in use in the United States. There are a range of existing public and private databases - we have already touched upon this morning - that offer the capacity for some insights to identify and investigate safety signals.

Now, none of these datasets are perfect. The challenge will be finding ways to bring them together so that we can reach insights that lead to valid conclusions as well as an understanding of what further evidence needs to be developed. For example, for this kind of distributed data network that we have already been talking about to operate effectively, there needs to be considerable standardization across the different data environments so that the same queries and programs can be run reliably across this broader national network.

Researchers will also need to determine the appropriate set of data elements for particular kinds of analysis and how to consistently analyze exposures and outcomes within the system and how to interpret the results generated. We also need to understand the strengths and limitations of some of the existing methods in pharmacoepidemiology which have not really

had to deal with problems of the scope and complexity before. In fact, Sentinel could lead to a new level of technical solutions and methods for developing evidence from medical practice.

Also important is communication with consumers and providers. The Sentinel Network is going to require some real attention to constructing a communications strategy to establish and sustain its positive impact on the use of medical treatments. Educating the public generally about the risk and benefits of medical products is already a high priority for the FDA. With the addition of Sentinel, new insights will be possible but it will also be important to assist the public in understanding these insights. What conclusions are appropriate? What further steps may be coming to resolve questions that remain unresolved? What are the implications for action? It will also be important to build a provider communication strategy that equips health professionals to interpret FDA risk communications as well as to answer questions from patients and consumers.

Finally, there are some very important legal issues, especially data privacy and confidentiality. The structure and function of the Sentinel Network will have implications for requirements around these kinds of issues. This has long been a key consideration for the FDA. For example, the emphasis on

distributed data methods that Janet described among other things minimizes any new sharing of patient-level information. This is an issue that is going to continue to require careful attention, and it will be important to set out a clear privacy policy as part of the communication strategy to make sure the public understands what is being done to keep their personal health information private.

So today, we are going to be going through these issues further plus addressing any others that you all want to bring up. This is a workshop format that will have a lot of opportunities for interaction and at specific points throughout the day, we are going to be counting on all of you to bring the ideas and the issues forward for the FDA to consider further in the development process for the Sentinel Initiative.

As you can see from the agenda that you all have in your packets, there is a three-fold purpose to the meeting. The first is to provide an update on the current status of the Sentinel Initiative and to allow for comments from a range of perspectives - we have already spent a bit of time on this, this morning; the second is to discuss potential governance models and their implications; and third is to discuss approaches to ensure continued involvement of all stakeholders as the initiative evolves. Both of these last two questions or bullets are very important where we need a lot of input today.

The next presentation on the agenda by Rachel Behrman of the FDA is going to provide an overview of what FDA hopes to achieve in working with others in relation to the Sentinel Initiative. Then Janet Marchibroda of the eHealth Initiative Foundation is going to present some potential options for discussion purposes here today to support FDA's objectives. After that, we have a short break. As you can see, we are running a little bit behind the schedule on the initial agenda - that is okay, we have had some good discussion already and we have some ideas in mind for making that up.

After the short break, though, which we will have, we are going to turn to a series of topical panels on the major functional areas of this framework for Sentinel implementation, and that is going to include data and informatics, legal and privacy issues, communication with providers, patients and consumers, and then scientific methods and operations. Each of these four panels is going to start with a brief overview that frames some of the key issues in each topic and it provides some considerations for the Sentinel governance decisions. Following these opening remarks, we are going to have some further open discussion for the broader panel and all of you here today in each of these four areas. After that, we are going to take a break for lunch. For those of you who ordered

or want to order box lunches, that makes it very easy to continue some informal discussions during this lunch break.

And then after that, we are going to have a breakout session that will start promptly at 12:45. This is an opportunity for smaller group discussion, at least relative to the size of the group in here today. And I want to emphasize, this is a critical piece; it is probably the most critical piece of the meeting. It is more of an opportunity than this large forum can provide to draw out and discuss any perspectives on issues that you want to make sure make it into this development process. So if you want to provide this very much needed input, please be in the room that is listed on the back of your nametag at 12:45. Within each room, there will be a discussion of one or more or all of these key questions that are listed in your agenda. They will be moderated by one of the panelists up here this morning.

Then at 1:45, we are going to head back here to have a summary of the breakout sessions from each of the moderators and then some further discussion. And then Janet is going to wrap this all up with some closing remarks and insights - I'm looking forward to hearing that too - and we will be done by 3:30.

So last bit of housekeeping issues after going through all that, this is a public meeting and so there may be some press

here in attendance. All this is on the record. The general sessions like this one are being audiotaped. The transcript is going to be publicly available on the FDA website. Some mechanics related to lunch, there was a mechanism for preordering box lunches online and you can pick those up outside this room and have it before you go to the breakout room or in the breakout room. Again, that is on the back of your nametag. If you did not preorder a box lunch, there are some extra ones I think available for purchase, and there is also a restaurant in the hotel and a few others just around the neighborhood here in Woodley Park.

We are going to have microphones in the audience throughout the day. You have already heard from some people in the audience this morning. Do not be shy about coming up for a question or a comment. Be sure to identify yourself though and let's try to keep it as concise as we can to maximize the number of people that we can hear from in this time together. Also for our panelists, there is a timekeeper - I'll introduce her in a few minutes - in the front row, who is going to do her best with my help to keep us on schedule, so keep that in mind as well.

We have a great, diverse, experienced group in the room today. I'm very much looking forward to a productive and stimulating discussion with all of you. And with that, let me

introduce Dr. Rachel Behrman who is the associate commissioner for clinical programs and the Director of the Office of the Critical Path Programs at the FDA to provide an overview of FDA's collaboration on Sentinel.

Overview of Governance Options

Rachel Behrman: Good morning. Let me first add my welcome on behalf of the entire cross-center team that is working on Sentinel, and thank you for setting aside the time and putting the effort because we are very much looking forward to this meeting. I will catch us up a little bit on time. I just want to reiterate a couple of points that were made but first, in terms of how to contact us, we will be opening a docket after this meeting and that is the best way to speak to the agency. It is official; it becomes part of the official record. In particular, since we are tight on time today, especially if it relates to just a particular firm or product, we encourage you to submit that to the docket and we will make that information available to all those who have registered for this meeting.

To reiterate some comments that Mark and Janet made, and to set the stage for Janet Marchibroda of the eHealth Initiative, who has been supporting us on this effort under contract in terms of both patients, consumers and healthcare providers outreach and the governance issues, as everyone

knows, FDA was mandated by Congress to ensure that medical products are safe and effective and appropriately labeled. The language is slightly different for devices and for biologics.

And also, we have the authority if indeed by any method or source of information we determine that the product is not safe and effective under the conditions of use, we have the authority to remove the product from the market. That is us doing our job and as Janet mentioned, we will continue to do our job. The question really on the table is sources of information. We all know an information explosion, a technological explosion; there are untapped sources of data out there. The time has really come and coincident with that, FDAAA provided us with a new mandate, new authorities with which we welcome.

So we will continue to do our job but as we have learned particularly over the last three years of the Critical Path Initiative, we can get places through collaboration that we cannot get to on our own. We can tap sources of not only information but experience, expertise and shared learning. So the thorny question is how to do that, how to put that all together in a very thoughtful and careful way. The way to make this not work is to do it in a rush, to be too ambitious, to not manage expectations initially. But if we do it thoughtfully and carefully and knowing that the Sentinel of

this year or next year is not the Sentinel of 25 years from now, we can really not only provide and develop a national resource and provide FDA with a source of information or sources that is qualitatively and quantitatively very different than anything we have ever had. As Janet mentioned, we have let contracts, we know how to do that. We even know how to let big contracts but we have never done anything on this scope so we have to do it extremely carefully.

But again, we believe - and we said this in many other contexts - that it is unethical to expose people to products that they do not need to be exposed to. So in a critical trial setting, it is unethical to conduct a clinical trial to develop information that already exists. And I think we would argue the same is true in the postmarket setting.

So we are really looking forward to a very active collaboration in terms of how to establish a national resource that will meet as many needs as possible. We understand under collaboration none of us get everything we want, and everyone gives up a little autonomy and a little control, and that is always painful but it can, as I said, get us to a place we have never been before.

So I think really with that and with the five-minute sign up, I will just again thank you for coming and acknowledge the enormous effort that both Brookings and eHI are doing in

support of us in this effort and turn it over to Janet Marchibroda.

Janet Marchibroda: Thanks, Rachel. As she mentioned, the eHealth Initiative Foundation has been engaged under a contract with the FDA to develop a set of options for the governance and operations of various components of Sentinel. So as part of that process, we are reviewing rules, laws; we are listening to experts, stakeholders like those in this room. And we are looking at experiences of other initiatives, and there are many in this area both inside and outside of healthcare.

In a few moments - and this is after our break - we will have the opportunity to hear from a set of experts and stakeholders who will offer their views, and as Mark said, governance follows function. What is it that we need to do? They will offer their views on a set of key high-level capabilities and considerations for creating aspects of Sentinel in four key areas: looking at the scientific operations; data, and informatics; the legal and privacy issues; as well as risk communications. And what we will find when we go there is that there are many activities that need to take place in each of these areas and many issues that need to be addressed - some by the FDA and some perhaps by stakeholders and experts outside the FDA.

Most of the activities that we will explore through these panels will require governance. As Janet Woodcock during her remarks earlier defined governance for the purposes of this meeting, as we think about this, as developing and implementing policies and procedures for both decision-making and administering certain aspects of the initiative and designing and maintaining identified capabilities and needed functions for various aspects of Sentinel, including those related to the four areas that I described. As Janet Woodcock and Rachel Behrman just relayed, there are many of these areas that are a part of FDA - I think you said - doing its job. It is part of their statutory authority; decisions about approval and licensing, risk identification and analysis and risk communication.

So we are going to explore as you think about governance, there is a broad spectrum and we pooled some definitions. In general terms, it really relates to decisions that define expectations, grant authority and verify performance. And when you think about it, when you look at what is happening in different initiatives both within our country and globally, this ordinarily occurs in three broad ways: through top-down methods that primarily involve just government, and there are many activities that occur that way. In some cases, you see networks that involve public-private partnerships or

collaboration of many organizations both within the public and private sector. And in our country, we often use through the use of market mechanisms whereby market principles of competition serve to allocate resources while operating under government regulation.

As Rachel mentioned, Sentinel will provide FDA with another very important source of information, another tool as it continues its statutorily mandated activities to ensure that our medical products are safe and effective and appropriately labeled. So again, thus we are not here today to discuss those decisions - the FDA decisions - and authorities.

But at the same time, it appears based on the experiences of others as well as language in the Amendments Act that there are areas related to Sentinel that would benefit: 1) by participation both within the public and private sector and potentially involvement of other organizations in areas of governance. One area in particular that may lend itself to thinking about different models is around the data, the information architecture piece. It is not clear that we will see a one-size-fits-all approach and it is not the expectation that when we leave at 3:30, we will figure out how to get there. What we would all like to hear however is this - as you delve into your four areas and discuss this both in the panels and within the breakout groups when we have a lot more

opportunity to talk, we would like you to think about the following and share your insights so we can gather those and this can provide really good input to the FDA.

If there are key areas or activities that fall beyond FDA statutory authority, where and how do decisions get made? What about structure, do we need an entity or a set of entities in place to support these decision-making processes? How do we engage the participation of others outside of government? Do they have a role in governance with some of these activities that may fall outside of FDA's authority? And what are the attributes of the governance that will build trust and make this work?

So we would like to very much hear about the different perspectives on how to move forward on various aspects of this as we move forward. And that tees up some of the discussion for the rest of the day.

Mark McClellan: Thank you very much, Janet. At this point, we are going to take that first break that I mentioned. It is about 10:15 now. If everyone could be back ready to go by 10:30, we will get started with our panel discussions. Thank you all very much.

[Break until 1:08:47]

Perspectives on the Potential Structures and Functions of Sentinel

Mark McClellan: All right. It is about 10:30 and as promised, we are going to start at 10:30. I do not have all of the lead panelists up here at the front of the room yet but they are going to get here shortly, and so we are going to go and get started. So let me ask everyone to take their seats and I would appreciate the conversations ending for the time being. We have lots of time for conversations throughout the day today.

So welcome back. As you all are taking your seats, this is the part of the meeting where we are going to provide some opening perspectives on key functions for Sentinel, those four major topic areas that we talked about before. And as a reminder these functional areas have implications for the structure and the governance of the Sentinel Program and that is what we want to discuss today.

I'm going to introduce our four moderators for the panel discussions and then they are going to introduce their panelists. I think since I do not have all of the panel leaders up here at the front yet, I'm going to go ahead and introduce all of them and hopefully, in the next 30 or 60 seconds while it takes me to do that, they will make their way back up to the front.

So to begin with, on my left will be Shawn Murphy, physician and Ph.D. who is the associate director of the Laboratory for Computer Science at the Massachusetts General Hospital. He is also an assistant professor of neurology at Harvard Medical School. He is going to moderate our discussion on data and infrastructure, so the first topic for this morning is data and infrastructure.

Then we are going to hear from Marcy Wilder who is a partner at Hogan & Hartson who will moderate our discussion on issues related to legal concerns and privacy. The third panel discussion will be led by Marc Boutin who is the executive vice president and chief operating officer of the National Health Council, who is going to moderate our discussion on communications.

Then finally, the fourth panel is going to be led by Richard Platt - right here on cue - who is a physician and professor and chair of the Department of Ambulatory Care and Prevention and a professor of medicine at Harvard Medical School. He is also hospital epidemiologist and attending physician at Brigham and Women's Hospital and a principal investigator of the HMO Research Network, and he will lead our discussion of scientific operations.

So we just about have everybody back, I think. Just a reminder of how the session is going to go, we are going to

have about 15 minutes max for initial comments by each panel's moderator and the panelist followed by maybe eight to 10 minutes for comments and questions from the audience. Again, this is also going to be followed up by those breakout sessions this afternoon where we want to hear in more depth from all of you. Please keep an eye - for all of you on the panels - on our timekeeper. So Elaine Duffy, meet all of our panelists. Elaine, can you wave? Elaine is going to have the signals to you on when to finish up, and I will be helping her out. So with that, let me turn this over to our first panel with Shawn Murphy.

Shawn Murphy: A good late morning to you all. I'm Shawn Murphy and I'm going to be leading this data and informatics panel in a very distributed fashion. Our data and informatics panel is going to focus on governance issues that arise in the context of our distributed versus central model for performing the Sentinel Initiative. A distributed system like we have been discussing comes with many governance problems that need to be addressed; some of them technical, some of them not. We will be talking about some of the more technical ones. So for example, when you arrange data in a specific way, how must that happen to facilitate similar kinds of queries and analysis? That is, how would we go about adopting some kind of similar data model?

Second, when you have codes in these databases, how would we discuss or govern what specific kinds of coding systems would be required at the participating institutions? And if we are to have a distributed system, which we will be collaborating on various kinds of queries that would be performed, how would that collaboration take place from a technical point of view? Certainly the idea of having just a big old con-call for us to try to facilitate that probably would not be enough, and so how would we govern that kind of facilitation and communication?

All of this then will boil down to how would that then all enable an analysis to take place on the network and how would that be governed from a technical point of view? So my panelists are going to be exploring the feasibility of these issues in the context of a central system versus the distributed system that we have been discussing. For that, Marcus Wilson is going to be the first then Vik Kheterpal next and then Sebastian Schneeweiss will be the last speaker.
Marcus?

Marcus Wilson: One of the things I think is critical for all of us as we embark on this endeavor - like everyone mentioned and Rachel, you brought it out - I think it is really important to reemphasize and that is, we really have to be careful not to let our endpoint get in the way of our starting

point. We can go many places with this over time but we have to really be careful that we do not wind up being now data-rich but information poor. And I think what is even more risky is that we really will not we are information poor, and I think any of us that have worked with databases, all the different electronic databases that exist today, realize that if you take it at face value, often you are wrong. And that is the problem we wind up with if we rush too quickly down this pathway so most of my comments are going to be along those lines.

I'll start by saying it - there is no one single data source that exists that has the size, the data elements and the population coverage that we would be able to use as the answer. So it necessitates that we bring together multiple different data sources to make this work. And I'm going to be careful not to use the term database too much because the term database whether centralized or even decentralized I think is something we have to define ourselves to make sure that we understand when we begin to work with different databases that we also work with our databases that have the ability to either enrich or validate the data sources they are inputting into that database.

If I use the example, one of the questions that came up in an earlier session from the audience was around data quality and claims data being a good example of that. I think the

things I'll talk about the principles are true for all data sources. There is no clean data source out there, and I would argue that clinical trial data are not clean either for the same reasons that we are doing this initiative here.

But if we think about a data source and we think about within Wellpoint itself, we generate roughly 1.5 billion claim lines a year as an organization and we have to remember the purpose of the systems that generate those data is to pay claims, not to do medical evidence generation. And so as we go about the process of generating medical evidence, we have to do so with great care.

And I will tell you, in the year that we have been working formally on building our own safety Sentinel Program within Wellpoint, the lessons that we are learning day in and day out on this are extraordinarily critical. And as we all sit around the table together to try to answer these questions, we need to be able to share that type of information. You can look at a question or try to answer a question on a risk around a product and just by changing the definitions of the endpoint, change the definition of the population or factoring in other types of issues; you can change the actual output of what you are looking at. And I think we have to have the ability to take the answers or the signals that we get in whatever systems that

we are using and get down to the source and validate what we are seeing to make sure it is real if in fact it is.

One of the last things I will comment on before I pass the mic over to Vik and that is just think about in the databases as we bring those together, there are apparent confounding factors that we can talk about some of the definitions I just mentioned but there are also many non-apparent confounding factors. If you think about it, just within our population alone, there are thousands - literally thousands - of different benefit designs that are meant to change treatment patterns. And so unless you look at our data with that in mind or have the ability to go back and say where was the former positioning of products and when did it change, what are the medical benefits that may change either how the patient flowed to the system or how the data were coded into the system - unless you can answer those questions, you would be very careful in interpreting the results of your analysis.

So in the end, I'll summarize by saying this. It is that really, let's not think so much about databases but think about data environments and finding ways that we can early-on link together those different data environments collectively, not physically linking them together but linking them together in the quest to answer specific questions. As we begin to do that, we will begin to answer some of these issues around how

we define a data model, how do we actually begin to over time pool together data sources into a more common format that will allow us to get higher level of quality? Thank you.

Vik Kheterpal: Excellent points. I think we are using a lot of terms and those of us in IT and informatics, it is particularly dangerous to use terms that other people have ever heard of before because they are very loaded; everybody has preconceived notions of what a database means and centralized versus distributed means and all sorts of physical and logical models come to mind based on our previous experiences. And maybe that is where I guess I start thinking about this.

I have five points I think that come to mind, just listening, which all came up in about the last 10 minutes, so a lot of preparation. One is I think we are thinking of the system as this monotheistic single amalgam and I'm not sure that is how it will end up being; that it is a single entity and a single way of thinking about it. I believe folks have already brought up there may be claims data houses, there may be payers, there may be health plans, and there may be provider organizations. And in that context, even though the interface to these folks needs to be universal, I think most likely in the real world, these things end up being more of a grid where our effort ought to be to match the data type with the intended kind of query you may wish to run. I think Alec brought up a

very interesting point earlier in the opening remarks to say if you are looking at CHF, claims data may not be good, and I think that is a general principle we may want to keep in mind as we go through these discussions to not to think of it as a single system but maybe a stratified system out there and step away from thinking of it as a single monotheistic system.

The second idea is we also continue to have this conversation as if it is a single-phased query because the word query says you send a query an answer comes and that is all we will ever do. And I think it is a multiphasic thing in the real world that these things tend to operate. Certain kinds of claims data for surveillance and generation of null hypothesis may work really well as an exploratory query against a claims-based dataset, and then we may have a peel the onion approach to subsequent queries to different datasets that may have a similar technology way of interacting with them that can do -- and so again, I would appeal that as we go through the dialogue, we maybe keep that in mind, that it is not a single query with the answer coming back and then we use some statistical technique to just amalgamate it all. I think it will be a little bit more iterative in a way. And I think that has implications on governance because the privacy disclosure issues may be different for the exploratory query versus the deeper ones.

A third concept that comes to mind is again, centralized versus distributed. I guess I step away from that a little bit and say for a moment, let's imagine it is one or the other. For a moment, it does not matter, each of them has some tradeoffs and we ought to be a little bit savvier about describing what we are gaining and what we are giving up in the discussion, and that would be a great place to get started as opposed to taking a position on it per se.

The position that I tend to come into the table a bit biased with is regardless of which one it is, I think the more important issue is whether the data for the consumers is linked or not. And by that, I'm talking about not linked as an amalgam, the idea, the way the U.S. healthcare system is organized, I'm very likely to receive a PayMed - I'll use that bad term, Vioxx I apologize. In my ambulatory physician office and that might be picked up in a PBM query because it got paid or in an ambulatory EMR but the likelihood is that I would probably go to a health system that uses -- that has no entity relationship and they use an EMR where my chest pain or my cardiac event was actually picked up in the ED. Unless I have some sort of a linking strategy by looking at these things - whether I centralize them or not centralize them - I will not pick up the right signal associations. So a lot of the chronic disease and manifestations of things we do that come over time

would be lost if we do not understand this issue. And I think it transcends centralized versus distributed as a concept.

The fourth concept is one of a technical informatics one. It is that with new architectures, we may want to think about it as more of a catcher-pitcher model. There are those who hold data that have to pitch it and there are those who have to catch the data. And there may be different roles to be played there and different mitts that we all hold in transformation that conduct. Again, in a service-oriented architecture - I think we have a CIO in Michael is sitting across the table - there are some very interesting things that are possible when you do that.

And the final one would be one related to guiding principles that really it would be awesome to have version 1 focus in after having a strategic conversation to a particular use case scenario or a particular thing we want to be able to answer by 2010 as opposed to in general and allow 1.0 to potentially be a throwaway technology solution but more importantly achieve some very important governance engagement with the public - those kinds of accomplishments that transcend and allow us to move to 2012. And I think that would -- again, in our experience, having functional pilots out there as early as -- you have to get very focused. Thank you.

Sebastian Schneeweiss: All right. Thank you. My first point, I think, is just really the logical consequence of what was said this morning already emphasizing the advantages of a distributed approach versus a centralized approach. I think you want to have a stable group of investigators who are really experts in that one data environment - I like that term - who really understand the strength of that data source, understand the limitations, understand the accuracy of that data source can do validation studies in that data source if needed, can drill down to individual patients if regulators need to do that, who also have developed algorithms and procedures to run data analysis and queries efficiently, know how to handle IAB issues, privacy and security on a local level. I think you need a strong local team, which really supports this distributed network approach.

At the same time, once you have a distributed approach, you have to standardize to some extent, and I know that much smarter people than I have worked extensively on these issues. But I want just to put out this warning that you do not want to settle just the smallest common denominator with regard to standardization because you want to draw on the differences and the richness of data between the different data sources that you have. You really want to see that, and what Dr. Platt said before that you might get different results in different

databases and then your task is to explore this heterogeneity. Is it that the population is different or is it that the information content in each database is different?

The third point flows from that to the extent that, how do we want to handle the confounding factors that we can measure in one database better because the information content is richer than in other databases? And there, I think the challenge will be that the patient data privacy and plan privacy as well, you want to share the patient risk mixed with other -- or centralized structure. That is in direct contrast to the need of multivariate adjustment, and I think there are lots still to be developed and discovered how to do multivariate adjusted analysis across several centers without sharing information that makes individual patients identifiable. So there is plenty of exciting stuff in front of us. Thank you.

Mark McClellan: Thank you very much, Sebastian and Vik and Marcus, and Shawn for leading this discussion. I'm going to turn to Marcy Wilder for our initial discussion of legal and privacy issues.

Marcy Wilder: In terms of data privacy, we have heard two important concepts this morning. One is that under Sentinel, there will be developed a nationwide electronic safety monitoring system in which data sources will remain with

original owners behind existing firewalls. And the second is that queries will be run and the data owners are going to convey the results of their queries to the network for analysis. We do not know yet whether or not the query results will be identifiable data or de-identified data or somewhere in between. That is one of the important issues that is yet to be resolved, and how that issue is resolved will direct, in large part, what kinds of privacy protections are called for.

We have in place a legal privacy framework and it truly is a framework as applied to Sentinel because it does not answer, does not fill in the walls, if you will. We have the Federal HIPAA Privacy Regulation; we have the Federal Privacy Act; and we have state laws that protect, in particular, sensitive information like HIV and mental health records. Each of those laws will have a part to play. In addition, I predict that some of the gaps that currently exist will be filled by legislation that we will likely to see this year. And so that is yet another set of unanswered questions. So whatever framework is put in place, it is going to need to be flexible enough to deal with the laws that currently exist and the laws that we expect will come shortly.

That said, FDA will have a great deal of discretion in terms of how to put privacy policies and protections in place for the Sentinel Program. Typically, privacy laws including

HIPAA, balance the desire to provide patients with some set of reasonable control over their records with public health needs. And again typically, like HIPAA does for safety monitoring, data owners are permitted to use and disclose the data for safety monitoring without patient consent or authorization. So because we are operating in a field where we believe in large part patients will not be consenting or authorizing these uses, we need to pay even more close attention to what kinds of privacy protections are in place.

Some other things we know are that the FDA is required to collaborate with public, academic and private entities to study advanced drug safety questions. That suggests the focus in each of those stakeholder groups is going to have some kind of access to at least some of the data. And HIPAA is going to permit disclosures to each of those entities to the FDA, to those regulated by the FDA and to others, both for public health purposes but also for public health research. And I want people to think about the distinction and understand the distinction between a public health use of information and public health research because I think that is going to be an important distinction that is going to follow us as we talk about what kinds of privacy protections should be in place.

I have said already that HIPAA is going to permit and the law is going to permit disclosure of de-identified,

identifiable data and data that falls in between. There are currently some protections in place. Before that happens, health plan members or patients are going to get a notice of privacy practices and they will be informed that their information may be disclosed for public health purposes. In addition, the covered entity is going to be required to disclose only the minimum necessary for the public health purpose, so there are some limits on what can be disclosed.

Finally, right now, if a HIPAA covered entity is the one providing the data to the Sentinel Program, there is going to need to be some kind of an accounting of disclosure so the individuals will have some recourse to see for what purposes and to whom their data was disclosed.

So I wanted to give that basic overview to say there are protections in place, they tell us some, they provide some protections but in the end, there are a lot of decisions to be made. And the questions we are going to be looking at today are: what are the protections that are currently in place; what protections should be in place; who will decide what protections should be in place; and who will protect the privacy of the data and those individuals? And then finally, we will also be going to want to talk about - maybe not today but as this evolves - enforcement mechanisms are going to be an important part of that discussion.

So with that, I'm going to turn to the panelists. We are going to hear from Carol Diamond then Deven McGraw and then Barbara Evans.

Carol Diamond: Thank you, Marcy. It is a pleasure to be here, and unlike my colleagues on this panel, I am neither a lawyer nor a privacy expert, so I'm especially grateful for the opportunity to be here today. I really want to share what we have learned over the years in Connecting for Health about information sharing to serve public good, improving quality and safety while protecting privacy.

What I found over the years is that very often in discussions of privacy, there is a desire to find the privacy policy that applies to everything; the one size fits all set of policies that will apply to everything from health information sharing between clinicians to e-prescribing to surveillance to safety, and of course that does not exist. I have spent many years learning that privacy is contextual and needs to be thought of in the context of how data is being used, for what purpose, how it is stored, how it is shared, who has access and the purpose for which it is being used. And this really does shape the ability to create detailed policies. They have to be created in the context of its use.

While there is no one size fits all set of policies, we have been very well served by a single common framework in our

work at Connecting for Health of key attributes that really set the bar, they create common expectations for what privacy policies and technology practices need to achieve. These common expectations or attributes were meant to apply broadly. They were meant to create flexibility, to set the bar but allow for detailed policies depending on the particular initiative. And I think this flexibility is really essential in any health information context. We have applied these basic attributes to some very specific things in our work in Connecting for Health, and the policies that emerged for health information-sharing are very different from the policies that emerged for personal health services. Those are two very different things.

So let me share with you what these basic attributes are and talk very briefly about them. The three attributes of the common framework are, first, a set of core privacy principles. We did not make these up, these are rooted in Fair Information Practices and some of the OECD principles, and they cover things like openness and transparency, purpose specification. In other words, what is the purpose of the data collection effort, collection and use limitation, individual participation and control, remedies, security safeguards, data integrity and quality. These nine principles basically frame the expectations against which people can create detailed policies.

The second attribute of the common framework is something we call sound network design, and that is to say that technology and policy should not be uncoupled, that there are ways to use technology to implement privacy policies, and there are ways to use technology to protect data. So this notion of a distributed system is certainly something that we have advocated where we keep data as close as possible to the source but allow it to be shared and analyzed under a framework of policies.

The third attribute of the common framework is critical and it is the issue of oversight and accountability. No framework is good unless it is adhered to, that there is an oversight mechanism and there is accountability for it. By the way, everything I'm saying is on our website. There is a policy brief actually there that fit frames this at connectingforhealth.org if you are interested.

We have taken these three attributes and we have applied them very differently to very different contexts, and I would argue the same could be true here. That the FDA could look at three attributes and say, what are the detailed policies that we need to develop against these expectations that allow data to be used?

I'm getting the stop signal so I'm just going to close by saying one of the things that I think is very important about

today is that the discussion about privacy and privacy policies is starting at the moment at which the network design and the technical issues are being contemplated. We have a saying in Connecting for Health, which is to say technology and architecture is policy; decisions about where data is stored and how it is accessed create information policy.

And it is very good that these discussions are happening now, but privacy is not a destination, it is a process. And I would encourage that privacy is included in the governance discussions, that it is developed longitudinally with the technology and architecture decisions that are made. Technology will be applied differently, different issues will arise, and that is the way policy needs to evolve - in coordination and in collaboration with that process. Thank you.

Deven McGraw: I'm going to play off Carol's comments a little bit because I agree with all of them and I want to just emphasize a couple more points. When I first heard about this and the thought of FDA being able to access data from multiple databases to do drug surveillance, I said to myself, "Well, that is a great idea, and the more that we can pursue that vigorously, the better." I think where we get nervous from a privacy perspective is when you sort of push out the edges of that and come to greater considerations of who will have access

to the system and for what purposes, and perhaps more importantly, who is going to decide who has that access and for what purposes?

While I agree with Marcy that we sort of have this baseline set of rules out there in HIPAA, it is a contextual set of rules that apply to certain transactions and for certain purposes, and what Congress has done here and what we are proposing to build here really opens that up in ways that were not contemplated and so we are going to need to be making these policy considerations all along. So consistent with what Carol says, this is a process and at every opportunity where you make decisions about who is going to have access to this data and under what set of rules, and how are we going to hold people accountable for how we use data?

So I think the questions about governance if this is going to be a public-private entity, how are the public's needs going to be best served? How are we going to ensure that this system operates if not exclusively then certainly primarily for public benefit? And then how are we going to hold people accountable for the data that they may be able to access? And then also with respect to how this gets financed in the long term, when you use words like ancillary sales of data, it is a little bit like waving a red flag in front of folks whose primary concern

is privacy but privacy policies that enable information to flow for the right reasons.

So I think these are very delicate questions, and I think what makes me most nervous is when we think about a public-private body that will be making these decisions. Again, how will we ensure that public benefit against the primary reason and that we have not -- this is really going to be a valuable source of data here? And how are we going to allow this to be used, and who is going to sit at the table to be able to make those decisions?

I think the questions that are coming up in this context are not unique necessarily to what we are trying to build here. They are also being considered across the country with respect to the building of health information exchanges, which is why, again, this contextual point that Carol made is so important. But we have seen the use of public-private entities to make these decisions and other context in healthcare with a bit of mixed results. And so I think learning from those examples will be helpful as we structure this.

I do not have any more detailed comments to add in part because we are at such a beginning phase of this but I'm glad that there will be a docket opened to allow us to respond to this. I hope that as there are advisory bodies created to move this forward, that there are consumers there who both care

about being able to use this data to improve health and improve drug safety but also to be paying attention to those privacy concerns.

Barbara Evans: The Sentinel System is the first major example of truly 21st-century infrastructure that Congress has authorized. Congress followed a regulatory model that has been used many times whenever America was building large, new infrastructure systems like a power industry or a telecoms industry or the Sentinel System. Over the past 120 years, this model has successfully protected the public interest in many different contexts. It is a good model and I'm confident it can protect the public interest here which is privacy. The devil though is in the details as FDA establishes governance structures and ground rules.

Among the complexities are that Congress authorized engaging the private sector to help finance and build the system and authorize safety studies that may involve outside academic and commercial entities. I'll mention just five points.

First, decisions about how to mobilize private investment are crucial to privacy. Infrastructure financing is a very well developed art and there is a lot of experience with how to attract investment while still preserving key policy goals. FDA's available governmental funds need to be deployed very

skillfully, and that may mean making some direct governmental investments in infrastructure but it also may mean using a whole array of other techniques like risk guarantees, tariff structures, and conditional loan guarantees. A well designed financing plan can unlock the private investment while bolstering the privacy policies. I frankly see the financing plan as a key determinant of how much privacy there is going to be.

Second, credible privacy oversight requires staffing and it requires resources. Governmental appropriations are almost always scarce and user fees may invite problems of public trust. The FDA may want to look at alternative approaches that have been used in other regulated industries. There actually are a number of alternatives for how to fund an oversight function. Also, smart governance can help reduce the need for big governance. For example, you could leverage FDA's own privacy oversight efforts with incentives for people who work with this system to come forward if they spot a problem. CMS has used strategies like this very effectively in some of its Medicare enforcement so there are good precedents.

Third, the system architecture affects privacy. You can almost always get more privacy by limiting the degree of dataset integration and reducing longitudinal linkage of the data but that undercuts Congress' public health objectives for

the system. A phased approach is probably the answer. Start out with limited integration while working to develop muscular privacy oversight that can support greater integration down the line. This is going to take some years and we do not just need a long-term plan for the system development; we need a long-term plan for how the privacy and governance structures need to evolve.

Fourth, privacy depends on a lot of nitty-gritty issues - things like should the ground rules be set by rulemaking or by contract or some of both. I will not list them all, I will just say there are a lot of these little issues and they are important.

The last point, public trust depends on the decision-making process. When FDA approves a drug, nobody is actually forced to take that drug but decisions about the Sentinel System are going to have a mandatory effect on people like us whose data may be in that system. Mandatory decisions require a very high level of procedural safeguard. There are well established norms on how to do that, they will just need to be adapted and tailored for use in this particular context. Thank you.

Mark McClellan: Thank you, Barbara, for that discussion. I think we will move on now to the next panel which is going to be kicked off by Marc Boutin who needs a mic.

Marc Boutin: Thank you. I would like to start off by explaining to the group that nearly one-third of the American population has one or more serious chronic conditions. And I would like to ask by show of hands for those of you in the room to raise your hand if somebody within your family has a chronic disease or disability like epilepsy, Alzheimer's, cancer. If you look around the room, a lot of hands were raised and I think the opportunity for this project that we are discussing is huge in terms of improving public health for all the family members that you yourselves raised your hands about.

But there are some challenges in this space, and some of those challenges include how and when to communicate. We live in a day and age where information is ubiquitous. We just spoke about privacy which is clearly a legal right, but when you speak with members of the general public, there is this emerging concept that access to information is an equally important right. People want information immediately and yet, you heard from some of the speakers earlier that there are going to be challenges of identifying when information actually indicates a real risk. How will we determine when we are going to put that information out to the general public?

Once we decide we have a good risk that we need to communicate, how will we going to effectively communicate that to the different stakeholder organizations that need to be

aware? You look at our provider community, you look at our patient community, you look at consumers in the general public, they are all different audiences with different needs. We know from research in the patient advocacy community that people nearly uniformly misunderstand risk communication as we currently do it, and we know the impact of those communications how tremendous challenges for people with chronic diseases. We see instances where people cannot get access to medications. We see prescribing challenges. We see adherence problems with people with chronic conditions. The implications for their public health can be tremendous, so clearly, we need to understand when we are going to communicate, how we are going to communicate to do this as effectively as possible with the best research to achieve the best outcomes.

There is a great definition of effective communication by Stephen Covey, and he says that effective communication is a balance between courage and compassion. The courage to speak forthrightly with conviction, with a compassion to understand the impact of that communication on the listener. I think that is our challenge here as with many of the other issues, it is to get the balance correct, the balance on when to communicate, how to communicate to achieve the greatest public health outcome for the constituents we all serve.

We have two people who will be presenting today; we have Fran Cunningham from the Veterans Administration and we have Michael Berkery from the American Medical Association.

Fran Cunningham: Hello. I'm going to take an approach I guess to further define what Marc just discussed, and that is when to communicate, and I want to add something else to that and that is to whom you communicate. Patients are important but so are providers, so are healthcare systems. And so it depends on to whom you are communicating as how best to do it, and it occurs at different times.

When we look at the Sentinel Initiative, it is a dynamic process or an iterative process. Just defining that or communicating in and of itself is not easy. I think it is easy for those sitting around the table and for those that have come to this meeting, but by and large, a lot of people, even our healthcare providers, will not understand the difference between the spontaneous reporting system that exists and the Sentinel System that hopefully will be in place. So I think that is the first thing, it is to begin to determine how best to define what this actual initiative is and to get the communication out from that standpoint.

I think the second thing is once that is known, and I'm going to stick with the Sentinel Initiative, is to look at and then define that that initiative is a continuum. If you think

of it from a Sentinel event or signal, we think of preliminary signal, signal strengthening, signal confirmation. In this era of evidence-based practice if you are in a healthcare system, you look at signal confirmation and you will not do anything until that risk has been confirmed. If you look at what we are trying to do, we are trying to make some type of a decision to communicate best what we are investigating during that strengthening of the signal.

And I think that is where this whole difficulty for risk communication lies. And I think what has happened to date even with some of the good work that has been happening with the FDA in communications is that I think more detailed and defined information is going to need to go out with risk communication as we move through that continuum of a Sentinel Initiative. So as you have a given drug and you are investigating certain things with this very good system that will hopefully be developed, we are going to have to figure out how best to get the information to our providers in a more defined method so they can continue to use and prescribe the drug in a given population that benefits from the drug while monitoring or limiting its use in the patient population that is at highest risk.

I think I'm not giving any answers at this point because I think that is a learning process, and that is going to be a

very difficult process that we are going to have to learn and live with and go through as we move forward. If I look at patients, that is another whole aspect. Take case in point, anything that comes in the newspaper, a patient is going to - perhaps you see it now - be very frightened, come to the practitioner or stop taking the drug, and I think that is what Marc alluded to earlier. So we are going to have to get information out to the patient to let them know especially as this goes forward, there may be unfortunately a lot of those things popping up in the newspaper and we are going to have to figure out how that type of information is conveyed to patients as well as to the media.

So I think when we look at communication from the Sentinel Initiative standpoint, there are a couple of points we need to remember: whom we are going to communicate; when we are going to communicate; and better defined communication and monitoring principles that go out with the different communication efforts. And keeping in mind that over-communication also can totally prevent the ultimate desire that you want one to have because people can then begin to ignore the major point that we are trying to get across.

Michael Berkery: I find it ironic as an IT person from a physician organization giving some thoughts on communication; it is like getting up to bat with two strikes, but I'll do my

best. First, I would like to underscore that we have a moving target, and as you determine where we are going on communication, the moving target is the quality of data we mentioned, it is going to evolve from where we are today to much better quality. The volume is going to go up of the information we have; it is going to up from 25 million to 100 million in two years and then much more after that. The sources of the information will eventually move from claims data to clinical data. And finally, the granularity of the information we have at hand is going to change and improve over time.

All those things as a backdrop, being an IT person, I would say we are not going to have one version, we are going to have many versions and then we are going to have to throw them away from time to time because they will evolve. And when I apply that to communication, I think we really need to focus on the communication as a robust function, not a series of here are the three steps we do.

Most of the people before me have talked about what are we going to communicate, when are we going to communicate it and to whom, what is the sense of urgency, and what is the education process for the physicians, the consumers and the patients. I think those are very important but given the backdrop of how this is going to move and improve over time,

this has to be a very robust function that really needs some strength and the ability to change as each one of those dynamics of the information provided through the Sentinel Project is going to change.

Mark McClellan: Michael, thanks for the comments, and I would like to thank all of you, Marc and Fran, for the comments from this panel. Our next panel on scientific operations is going to be led of by Rich Platt.

Richard Platt: My colleagues in this part of the discussion are Alec Walker and Joseph Selby. We actually prepared a slide so if it is convenient to put it up, would you, please?

Now before you look at the slide, let me ask you to close your eyes, imagine that it is 2012 and there is a robust distributed network in existence that has agreed upon rules of operation; it has good communications policies and excellent privacy protections. So now you can open your eyes and take a look at the things that we think Sentinel 1.0 might be trying to do and the things that would be part of that discussion.

So we will talk about three activities that we understand the FDA to intend Sentinel to be doing. On the left are rapid response; in some parts of the public health community, that is called situational awareness. There is the supporting and refuting of suspected problems; hypothesis testing, the formal

studies that inform us about the safety or benefit of compounds; then there is an active surveillance component that has been an important piece of the equation. I'll spend a couple of minutes talking about active surveillance. Alec will talk about rapid response, and Joe will talk about supporting and refuting suspected problems.

The things that are going to be common to all of these are the ones on the left-hand side of the slide. I would say intrinsic to extracting information as Marcus said, from data, are the fact that in our experience, the fact that there are so many combinations of therapeutic agents and indications for their use that we are going to need quite a lot of protocols to deal with them, so that for some considerable period of time, it is going to be important to develop and implement individualized protocols.

Secondly, as Sebastian mentioned, we are always going to have to deal with the fact that there are some important confounding factors between the reasons that therapies are chosen and the effects of those therapies and disentangling them is a complicated business.

The bottom four points on the left hand have to do with the way the network might perform. Marcus pointed to the fact that information sources vary between one another and over time, and that is I think going to be a constant feature of the

data sources that Sentinel depends on. We are pretty much agreed that different data sources will have different kinds of information and there will be considerable work in learning how to put those kinds of information together in a coherent way. We have talked about the fact that it is usually important to obtain additional information from a small number of the individuals whose information contributes to a variety of analyses. In claims data, that often means going back to original medical records. Even with electronic health records, sometimes it is important to get more detailed information either from the provider or occasionally from the patient.

And finally, as Sebastian noted, there are a number of methods that we do not yet have. Now, in thinking about active surveillance, I would postulate that it is both easier and harder than the rapid response and the supporting and refutation of problems. It is easier because the number of possibilities that we have to attend to is considerably smaller.

It is our expectation that FDA would be interested in doing active surveillance on a relatively circumscribed number of therapies at any given time. They might be recently released treatments or they might be things that are of particular interest and that the major focus would be on a relatively small number of outcomes. The kinds of things that

have been problems for -- in the case of drugs, many drugs that have been withdrawn from use, things like hematologic injury or renal injury or dermatologic injury or problems that are known to affect a particular class of agents or problems that arose in the pre-marketing evaluation of a therapy.

So the number of situations is much more circumscribed than it is if you want to use the system to respond to some concern that arose from some other situation. And so the notion of the mechanics of actually constructing a set of distributed analyses where each of the participating partners contribute certain kinds of information on a regular basis is tractable and we could imagine doing that in the early phases.

On the other hand, as Ginger Rogers said about dancing with Fred Astaire, she had to do everything that he did but she had to do it in high heels and backwards. And doing active surveillance means you do not have the luxury of taking your time to make sure that you are getting it right. You have to get it right, but you do not have the luxury of time because you are doing this more or less in real time. You are doing it across organizations for whom the data are fresh, and so when Marcus says we are always looking at our data and trying to figure out exactly how to interpret it, that has to be done in a very rapid way.

Secondly, Fran was exactly right, this kind of work is going to be done with a need to communicate the information, and there is going to have to be a series of decisions about where the set points are. Do you care more about being very quick to find a problem that is really there? In which case, you will surely have a larger number of false positives to deal with. Or do you set the threshold higher and understand that you will be somewhat delayed in understanding where those problems are? The implications of those decisions are both policy and methods and the way this is implemented.

I thought the previous panels did an excellent job of talking about the fact that there will be an urgent need to obtain more information from the signals that arise from an active surveillance program and then to have policies about communicating them that everyone will agree are doing justice to the need to have safety without concerns that diminish the ability of the medical care system to deliver good therapies.

So first thoughts on active surveillance, Alec is going to pick up on rapid response.

Alec Walker: My comments are going to really address real time uses of the data.

Let me illustrate rapid response by an example. Three years ago, there was a question as to whether a new meningitis vaccine was causing cases of Guillain-Barré syndrome, a rare

neurological condition that can be quite serious. Roger Davis of the CDC spent an anxious week calling different data sources to find out how many cases of vaccination they had and how many GBS cases. It turned out that there were none out of several hundred thousand. That was an example of situational awareness. It changed the heat of the question. It did not rule the association in a route but it made it clear there was not an impending public health emergency. The Sentinel System will be useful for that as well as for active surveillance.

The two pieces that I want to lay on the table and then work on how we resolve them is that the Sentinel System will not be definitive and will not be a reference system to use on the terms that have been put out today. On the other hand, that lack of definitiveness is not an obstacle to surveillance usage or rapid response. I think we can entertain those two thoughts simultaneously without too much cognitive dissonance through three steps.

The first is to consider the data for what they are, that is, in their native form we are not talking about myocardial infarctions; we are talking about hospitalization with an ICD code of 410. We are not talking about Stevens-Johnson syndrome; we are talking about hospitalization with serious skin rashes that might be compatible with that. As long as we are clear that we are not tabulating medical conditions but the

healthcare activities that further have to be considered and interpreted, I think that we right away reduce the over interpretation of data.

To use Janet's UN example, these things do get translated across systems into a common language, but I think we should think of that common language as Esperanto rather than English. It is a language of poor associations, rather specific meanings but none of the richness of a native language. By comparison, I would say that these things do not translate into medical knowledge; they translate into health services information. As long as we bear that in mind, we can talk about these things without too much fear of being over interpreted.

The second point in using these for surveillance is recognizing that the heterogeneity between systems, as several speakers have said, is actually a source of information. To draw a metaphor from my statistical colleagues, I would like to think of the difference between a fixed-effects and a random-effects model. The fixed-effects people want to go and look and see what is different about the different sources that cause this. In random-effects, we simply accept that there are things we are never going to know that are different in this more than traditional standard error calculation; it is going to be the source of our understanding of how uncertain our knowledge is. I think that just needs to be laid there and I

think that it is very useful for the system in keeping us modest.

In the context of those two, I think it is okay to adopt a position of radical transparency because we are just doing very low-level mechanical things. The scary stuff is high level and interpretive and is not intrinsic in the Sentinel System. And with that, I'll stop.

Joseph Selby: Thanks. If the Sentinel becomes a network of data sources that are put to the uses of surveillance on the one hand and rapid response on the other, it is very predictable that no matter what decision rules we put into place, the number of signals that require what we all think of as the more traditional hypothesis testing studies are going to increase, so we are going to have more signals to come to grips with. I think we all hope that the Sentinel, in addition to being a surveillance system, will be a better framework for rapidly and efficiently conducting hypothesis testing studies as well. Many in this room have been involved as I have in hypothesis testing studies. I suspect you will agree that each one requires really extraordinary amounts of discussion and decision-making that is unique to the exposure and the outcomes under question and to the biases that come along with it.

I was going to actually spend a bit of time elaborating on these issues, but comments by Marcus and Sebastian and many

others convinced me that much of this is appreciated, so I will be very brief. The activities preparatory to doing a hypothesis testing study are going to require choosing the analytic design and the steps to check and adjust for biases. Having considered that, next falls to the researchers to identify the data sources within Sentinel that are actually adequate in terms of richness and quality of the data, that they will support this measurement and adjustment for biases. This requires a keen knowledge of data sources as has been mentioned already. It requires decision-making about the trade-off between using larger databases which may lack some of the data detail but offer larger numbers of exposed persons, greater number of outcomes versus opting for smaller data sources within Sentinel that have richer, higher quality data.

And then, it requires specifying, as Rich pointed out, what additional primary data collection is needed. Do we need to verify outcomes by looking at hospital records? Do we need to link to mortality data? Do we need to survey patients to find out about symptoms, quality of life or to quantify exposures such as occupational exposures or more detailed smoking information?

But as I said, I think all of these are pretty substantially appreciated in this room already, so I'll just make two points in closing. The first is that I think we can

hope that there would be two stages, actually, in hypothesis testing that we can envision. Perhaps, the first stage could actually be done with these standardized data systems held by institutions that are participating in Sentinel. Depending on the content and the context and the question, these data may sometimes be sufficient to perform a preliminary test of the hypothesis. And perhaps, especially when the signal that we are worried about is not confirmed; it was just minimal or modest adjustments using data already in the system. But then, there will certainly be the second stage which will be conducted very likely in a subgroup of Sentinel contributors that are more detailed and that are conducted using more efficient study designs in a smaller number of settings.

Finally, in closing, just to sound to on an optimistic note that I think that I heard Marc suggest before me that over time, we may actually standardize some of these steps in hypothesis testing. We may gain an increasing sense of what study design or designs are adequate, what combination of study designs might together convince us of the validity of our findings. We also, hopefully over time, will gain further experience on the validity of various outcomes, so that some outcomes, as Alec alluded to, we feel very confident about without any further data verification. And also, gradually

gain a similar sense about the validity of some exposure data sources, at least in some data systems. Thanks.

Recap of Charge for the Day

Mark McClellan: Joe, thanks for those comments, and Alec and Rich as well - very helpful slide. I would also like to thank all of the panelists for their efficiency. We are keeping on schedule for this part of the meeting, thanks to their ability to convey a lot of useful information in the small amount of time.

Now, I would like to open this discussion up a bit more broadly to add some more perspectives in. You have heard now about four key functional areas related to Sentinel. All of them -- the discussion of data and infrastructure; the discussion of legal and privacy issues; the discussion of communications issues; the discussion of scientific and methods issues -- all of them have potential implications for Sentinel structure and governance, and all of them, hopefully, will help inform the more detailed discussions in the breakout groups that are coming later today. Those are going to be cross-cutting across all four of these different areas.

Now, to provide a little bit of a warm up for that, we have some time now to get some comments, reactions, further thoughts based on what you have heard already. You heard some fairly clear ideas about challenges and ways of addressing

challenges in each of these areas. You heard a lot of discussion about both the role for the FDA in areas where it has clear statutory authority in guiding and overseeing Sentinel but also a lot of discussion of public-private partnerships as reflected in the legislation or reflected in some of the functional areas and solutions to problems that you heard about from the panelists.

I would like to open up this discussion, now, to those who are here. Let me start, not to put you on the spot, but maybe turning to some of the FDA leaders who are on my right to see if they have some initial comments, clarifications, points that they would like to make.

Rachel Behrman: I would actually like to ask the informatics, the informatics kind of question or actually a sort of a nested question in the spirit of the panel. Let's say for argument's sake that we think about this and we come up with something that Sentinel looks vaguely like a safety component that is FDA's broader safety component that is done under partnership. Is it feasible to expect that there be a shared architecture? Is that achievable? If so, what does that mean to you? Shawn, you have said that is more than a conference call, so what is that?

And then, finally, knowing this is highly speculative and very resource dependent, if we are thinking about version one

and trying not think about it as a throwaway but as a step forward, what kind of timeframe might we be talking about? To get a little bit concrete for a start.

Shawn Murphy: Right, there is nothing like a difficult question from FDA. Exploring feasibility and getting into the weeds of data architectures, certainly, taking our hospital systems and doing an analysis within the data structures of our hospital systems is not really feasible. They are not built to be analytical systems; they are built to be transactional systems. So certainly, one would need to take the data out and put it into a different analytical system and that has been the strategy of most people here I think who built data warehouses and so forth.

Now, there is some convergence onto the data architectures that those data warehouses have and usually it is in something called an EAV structure, which is an entity attribute value structure. There are various models that the government has funded for putting together those kinds of structures so that the possibility that you can put together a common architecture that would give more hope to the idea that you could distribute a query and run it in various systems and it would be more or less asking the same question could certainly be satisfied with work in that area.

There is also, of course, the problem that different systems have different kinds of data and that the data is represented in different ways. We have different tiers of data. We have claims data, we have labs data, we have data that comes from electronic medical record systems and we have data that can be culled from systems using natural language processing or other forms of data extraction tools. Each of those comes with their own difficulties with coding them and representing them, but these are also fertile areas for exploration and curation. So I think that those problems can also be solved.

At the end of the day, I think that the vision that the FDA has that you can keep the data within an entity and yet operate upon it as though it was one large system is valid. That with appropriate governance and what is really key is the appropriate communication amongst the entities because now it is going to be completely dependent on that because they are not going to see each other's data. They just have to communicate and that is going to be very, very important. I think that is going to be very key to establishing and working out this vision. But having said all that, it does look very promising.

Mark McClellan: Thank you. Janet?

Janet Woodcock: Well, I want to congratulate the panel as I thought the explanation of each one of these issues was extremely lucid. It really helped my thinking a great deal.

I think what is emerging here is what we are talking about from a technical point of view from both privacy, as well as architecture, as well as the actual science that is being done is we are not just going to have one system that can only do one thing. We are going to have a series - whatever - conglomeration, and there will be fitness for purpose in the privacy application as well as what analytical efforts are actually pursued and in what systems they are pursued in, it sounds to me, would be driven by the problem, by the nature of the problem and the nature of the ability of whatever datasets exist out there to solve that problem or address the issue or what have you.

I think from my point of view, that provides a very nice framework of thinking through some of these things. That there is a graded tier of different activities that might occur and they would occur in different nodes or whatever. They would have different, perhaps, policies associated with them depending on what scientific activity are being done, depending on how close to the patient you need to get with your inquiries and so forth and so on. So I really appreciate all these inputs; I think it is very illuminating.

Mark McClellan: Thank you. Let me ask if any of the other panelists have comments on this and maybe just picking up on Janet's, Vik you mentioned I think this concept of use cases as a starting point for both the governance and the structural activities for Sentinel. That fits with what Janet just said about there may be a few key types of initial activities or undertakings that are feasible with different kinds of available data. We seem to define those better and come up with a proper structure for overseeing how they are executed. Joe talked about different levels of signal detection and confirmation and follow up. Can I ask the panel, does that ring correct for many of you here?

Vik Kheterpal: Look, in this context, to do anything within a given provider organization by June of 2010 might be considered not viable. So living in the real world, Marcus mentioned we may want to disassociate a little bit what we want to end up at from where we need to begin and also serve as more of an anchor point where we do live today and the reality is to get something viable up and running. In that context, I think having a use case scenario of certain kinds of things so we take the conversation for Sentinel for at least 2010 and 2012 quickly from strategy because that sounds like boiling the ocean a little bit. It is the stuff that I have been -- out of clinical medicine for 18 years, this is what I thought I was

going to do in '89. We are not very close to it yet, put in a Google search into this thing and it comes back and gives you the right answer.

Having said all of that, I think the trick in having something much better than where we live today which is, you know, somebody having to pick up the phone and call after a week to say can you run this query and so on to something much, much better is certainly possible, but only by getting very focused in it. That is sort of my piece I guess on not being monotheistic about how we define this thing.

Mark McClellan: Thanks. I have a comment here and then--

Howie Gallo: I'm Howie Gallo [phonetic] from MIT and the Safety Surveillance Group. I think this is amazing and wonderful, but let us take the metaphor a little bit. Even if the UN is created and world peace happens, I have a real significant worry in that. However you look at it, these databases are retrospective; they are collected for other reasons than the questions we are going to be asking.

In the preclinical sense, getting approval based on retrospective data that were designed for hypothesis or ask questions that it was not designed to ask, you would not appropriately so get approval for the drug. Here, my worry, my caution, is to take a drug off the market from this retrospective view, particularly if we get past all the

translational, all the mechanical issues - I assume we will - then looking at the data from that perspective to make a significant decision to put the drug on the market, retrospective data is not appropriate - and rightly so. To take it off, the question is why should it be?

Now, the realities are -- I certainly do understand the postmarket realities that you cannot do - unless you are a vaccine company - a 50 thousand controlled trial, but all I want to do is voice the caution so that the wonderfulness of having this amazing revolution in available data over the spontaneous dataset is substantial. I do not even have a question; it is just a word of caution.

Mark McClellan: Comments are just fine for this meeting as well, so thank you for that. Yes, Carol.

Carol Diamond: I want to pick up on this issue of stratifying policy and shift to technology for a minute. And maybe some of the folks who have been thinking about the technical aspects can think about this, or if this work has been done, I would really be interested.

One of the advantages of having distributed networks is that you can bypass the time it takes to collect all the data and normalize it and create a central data model and do all that stuff and clean the data. But if you push that all out into the edges, it creates an enormous burden on the people who

have those systems. I'm wondering if there is a way to think about this - I'm assuming you already have - in terms of being able to do some things in the absence of that.

And I'm reminded about the distribute system for flu surveillance because in this system, which is run out of the New York City Department of Health but is a national system, they decided not to even normalize the definition of ILI, influenza-like illness. They decided to just let people define it any way they define it and report their counts. But, they had a way to validate what they were finding in terms of trends because they were able to compare what they were seeing against CDC's flu surveillance graphs.

And I'm wondering if there is an opportunity to look at - because I think this issue of validation is critical - how good is this data at finding truth. I wonder if you have contemplated a sort of incremental approach where you work against some things you might already know and see if in the absence of normalization and standardization of everyone's underlying datasets, you can find this signal-to-noise ratio and know where you want to hone in. I guess it is a comparable question on the technology side as we have been discussing on the policy side.

Janet Woodcock: Just for people's information, a number of the pilots I mentioned are actually doing that, so those are

methodologic pilots in general that say, can you find known things in using a new methodology? We will see. These pilots are being done and they are trying to fish things out of these databases that we know about already.

Mark McClellan: It sounds like another good initial step. There is a comment down at the end of the table and then I want to go to the microphones.

Cherif Benattia: I'm Cherif Benattia from Vertex. My question is to Marc Boutin and the communications panel. But before that, I would like to say that I have been very pleased to see the communication piece on the agenda. Usually, it is always the forgotten piece of risk management, so I'm very happy.

So you have asked two key questions, when and how to communicate. My question is what to communicate? That for me is very important. Is it the data information, identified risk or confirmed risk? Who defines the risk and gives the recommendation?

Marc Boutin: Now, I think your question is right on target. The challenge of what you communicate and how you communicate are going to have implications for how patients comply or adhere to their medical regimens. I think what I'm trying to put into the mix here is we have to be cognizant of the communication strategies on public health more generally.

It is not simply being transparent and dumping information out. That kind of communication strategy could do more harm than good.

So I think your question is right on target. I do not have an answer specifically to it, but I think those are the questions we have to grapple with and come up with solutions that balance out the need that people perceive to have more transparency with the need to actually have positive impacts in terms of public health.

Mark McClellan: Now, do you have an answer for this? Is this something that should be incorporated maybe as part of these initial use cases that -- [cross-talking]

Cherif Benattia: I do not have a clear answer because the question is if you start thinking about what to communicate is also what to communicate in the format that people could understand and do something about it. If you take an example that at the request of the Congress, FDA is now publishing every quarter a list of drugs with the risks, but on the same page, the same information says that patients should not stop their treatments. So we found [indiscernible] that this drug has risk and at the same time it should not stop their treatment. How do I manage this information? So it is not easy, and I think that is why risk communication have been lobbying for years and they would love that FDA or some other

groups take the lead in implementing some good risk communication practices that take into account literacy, the audiences - different audiences if you want.

And I would like to end maybe with one more question to FDA or people here. We are focused a lot on Stevens-Johnson syndrome or other very severe drug reactions but we all know that around 50 percent of serious adverse events reported to FDA are preventable and this is real information. Is there any initiative or anything we could do to start at least preventing what is preventable and maybe just by some communication?

Janet Woodcock: Yeah, that is a separate subject. Obviously right now, we are focused on detection and analysis and learning about these but FDA will be launching in the new year an issue around safe use, which is going to be directed at partnering with many of the same groups to improve the appropriate use of medicines, which basically means preventing preventable adverse events from happening.

Mark McClellan: Thanks. Now, we had a comment on this comments on this subject from Fran Cunningham and Jesse and then I do want to go to the microphones to wrap up. So, Fran did you --

Fran Cunningham: This is just going back briefly to what do you communicate and when, and you asked a very good question and that is all of the above. We have to communicate all of

the above and when and what time is what we are trying to figure out now.

I think the biggest thing that we need to realize and that needs to get out there is that as we communicate risk at this point in time, it is very close to definitive and with the Sentinel Initiative, it will not be. And the risk information and the information that goes out there will be changing and that we are going to have to find some kind of way to educate our providers of that, educate our people that are heading healthcare systems of that, and then having a good way to interact with consumers so that they understand that this information will be coming out not to stop the agent [sounds like] and I think that is going to be the biggest difficulty.

Mark McClellan: Jesse?

Jesse Goodman: Thank you. On that, I was going to add that to the extent as you do a particular study or monitor a particular product that we apply some scientific principles to risk identification, it is important. So can you prospectively, for example, set some triggers or endpoints based on the quality or lack of quality of your data ahead of time and hold yourself and your communications team to those?

So again, apply the rigor of clinical trial and the uncertainty and quality of problems with these data to defining some of these communication triggers prospectively, I think,

can be very helpful. And we are going have to learn to communicate about uncertainty, which is one of the things that physicians, patients and the public as well as the FDA find very difficult to do and understand.

Mark McClellan: Thank you. We go to the microphone.

Kate Gelperin: In the past year --

Marc Boutin: Can you identify who you are, please?

Kate Gelperin: I'm Kate Gelperin, FDA. In the past year, we had the experience of rapid response situation for tainted heparin and that came to the attention of the American public due to an astute group of clinicians at a pediatric hemodialysis center and then this was investigated by the Centers for Disease Control and then ultimately partnership with the FDA so that a real time true rapid response scenario unfolded and I think that lives were saved.

I was somewhat concerned to see that even though Rich Platt's side says we should think about this being 2012 that rapid response figured prominently on the slide as something that the Sentinel might provide in 2012 and I think as Joe Selby pointed out, the specter of many, many false positives would really preclude an effective response such as we saw to the tainted heparin this past year. I would be interested in hearing a really honest discussion about that and also a personal plea that the experts in the room not hype or oversell

a very valid initiative, the Sentinel Initiative, but one that is not expected to replace the current systems and I think should not parasitize [sounds like] them.

Mark McClellan: Okay. So how do we prevent too many false positives from getting in a way of needed rapid responses?

Richard Platt: Well, I think part of what we are going have to do is understand what the performance characteristics of these systems are. In the same way, we -- a nice news article about the fact that magnetic resonance imagery identifies a whole raft of incidental illness and I think we are going to have to understand where the incidental illness are in the distributed network before we turn that loose on changing public policy.

Mark McClellan: Alec, your comment.

Alec Walker: Yeah. Noise in surveillance systems looks like noise when you come down and look at the individual cases. I think this false positive bogeyman has been stalking this field for a long time and I think it is overplayed.

Mark McClellan: All right, next comment?

Mel Greberman: I am Mel Greberman, Public Health Resources. First, I am very pleased at the emphasis on public-private sector collaboration. I think that really is essential.

One thing I wanted to bring attention to is an article written on December 11th of this year on safely implementing health information and converging technologies by the Joint Commission on Accreditation of Healthcare Organizations. In this article, they really deal with a lot of issues that are very relevant to the real world implementation of such systems as it will have a very strong relation to what will be required in implementing in the real world the Sentinel Systems, and I think it will be useful to really look at some of the issues and it includes the steps that the Joint Commission has already taken in this area and then really very nice voicing of many other issues that they feel need to be addressed. Since I did not hear their name mentioned as one of the participants, I thought I would bring that up and ask, have you had some contact with the Joint Commission on this issue and I think it will be very helpful.

Mark McClellan: Yes, a good point and I think more generally on this point as you all are thinking about comments here and in the breakout session is this question of what are the particular worries to look at in this public-private collaboration and oversight? It is very important for helping FDA along with this process. Anna?

Ana Szarfman: My name is Ana Szarfman. I work at FDA. I touch the data, I touch clinical trial data, spontaneous

reports and electronic medical records and uncertainty can come in different flavors; the uncertainty of having too many false positives because there is no adjustment for multiplicity and small counts. Uncertainty comes also from how we manipulate the data and the decisions made that are not very transparent and could also come from errors in one line of code in statistical method.

Then what I would like -- we have had a lot of success building automated analytical tools that results can be reproduced. There is not going to be the definitive answer that is like having an SAT score to assist, to have some common method that is a startup method that we can all use the same methodology applied to different databases and that we can understand the outputs, and then we can understand better the data decision that can change these outputs. Thank you.

Mark McClellan: Thank you for the comment.

Lawrence Grylack: Thank you. I'm Lawrence Grylack with PAREXEL consulting. There is an expectation from product sponsors for submission of risk management or risk minimization - risk management - take your choice of phrase. I would like to ask the panel particularly the FDA representatives as to how they see the Sentinel Initiative influencing our ability to advice product sponsors in their submission of these risk minimization plans.

Janet Woodcock: Well, I would say we have to get to a version 1.0 first.

Lawrence Grylack: Okay, fair enough.

Janet Woodcock: Yeah. You know obviously, we have heard different comments just in this comment session about to what extent this will be usable to answer questions in the near future, and I would think that it is going to be usable to answer some questions and it is not going to be usable to answer many questions right away and we have to pick the use case or whatever what we are going to address first. So over time though, I think to your point, one hopes as we evolve to something more powerful that can actually really be able to assess what is going on out in healthcare with the introduction of a particular product and at that point, that might be a very usable tool.

Lawrence Grylack: Thank you.

Mark McClellan: Thanks. Question over here?

Arnold Kuzmack: I'm Arnold Kuzmack, an FDA patient representative. It is a very simple yes or no question. The FDA being the Food and Drug Administration, is there any thought doing a smooth [sounds like] stuff on the food side of that?

Mark McClellan: That is a question for whom?

Janet Woodcock: Probably for me. Yes, to the extent that these data would be accessible, would have relevance to any question. Generally, the kind of data we are talking about now are not going to be that relevant but in time, as we just said in the previous question, the system and the data they are in that are reached may have relevance for other issues.

Arnold Kuzmack: But are the food people thinking about what is relevant for their situation or this sort?

Janet Woodcock: I mean this really is a truly cross agency initiative as part of our overall attempt to create enterprise-wide solutions and not siloed solutions as may have been done in the past, so the Center for Food is part of the group and we are thinking about that and ultimately, certainly technology should be applicable.

Mark McClellan: Thank you. Is there a comment over here from the panel? No, okay.

Jesse Goodman: Mark, I have a question.

Mark McClellan: I'm sorry. Jesse?

Jesse Goodman: Yeah. Just on that question of how do you advice sponsors. I totally agree with Janet, this system is not at a point where it is data. However, we have invited sponsors too. When we have access to postmarketing data, for example, for a new vaccine, we have suggested that they develop data, which is complementary. For example, uses different data

sources, different populations to again bring diversity to our postmarket assessment, so I would say this should be part of the postmarketing surveillance plan. The data FDA has and the data the sponsor brings and not have it be duplicative but to be greater than the sum of the parts.

Mark McClellan: Yeah, and some of the sponsors are using data sources like the ones contemplated here for Sentinel. So, you know --

Orville Kolterman: I'm Orville Kolterman with Amylin Pharmaceuticals. First, I would like to thank you for being able to participate in this and listening to this very rich dialogue. My interest is in the communication of this information and sort of have a synthesis of a number of comments that were made here, been made in terms of what, when, how and then particularly, as it relates to the maturity of the signal and as we bridge to this exciting new approach that has great opportunity.

I would hope that we would pay some additional attention to something I do not think is done particularly well now and that is that when we have a signal, you identified, have a discussion around basically what I would consider to be an analysis plan. How can we better evaluate this signal? What data sources should we look at and what is the relative priority? The thought about all these different data sources

becoming available and having different analytical experts with different expertise, the wrong expertise getting married up with the wrong dataset could lead to some even more interesting time than what we have seen now.

And then the second comment, this relates to communication. I think some of the comments could have a bit implied an attempt to communicate to a segment of the population like providers versus patients. I would just issue a plea for caution there because in this electronic day of communication, I'm not sure that there is any such thing as a selective communication now. I mean in my world, regulatory communications, safety communications, clinical communications, academic communications, investor communications and the like press -- all get mingled up and mixed up and muddied very, very quickly and things bleed over from one to the other. Thank you.

Mark McClellan: Thank you. I think we have time for one more comment or question. Please go ahead.

Mary Pendergast: Thank you. I will try to be quick. My name is Mary Pendergast. I'm a lawyer in private practice. I want to encourage you as you build this system to not let yourselves off the hook. I have heard this morning comments such as, "We want to get it up and running." "We are going to learn as we go." And my suggestion is that you got to have

some things in place before you begin and not wait until you learn as you go.

The two areas where I think it is really important is in communication. I think the FDA needs to acknowledge that the communication system at the moment is broken, that when patients learn of a signal, they often stop taking their drug. And I think that you have to recognize that you need to fix your system on how to communicate before you add more information into the alert system. I think a test would be - and it is a useful test always for the FDA which is - if the shoe were on the other foot, and if industry were saying the same thing, would you consider it honest communication or false and misleading? Just a way of thinking about what you are saying.

My second point is that - and it echoes something I just heard - what you have to establish a system in advance to figure out your paradigm, your algorithm, your cheat sheet on how you are going to resolve the questions that you raised. Answering unanswerable questions is not of benefit to anyone. When I play poker, I have a cheat sheet - two of a kind, three of a kind, two pairs, full house, whatever - and I doubt [sounds like] that if I'm here, something can beat me. And I think as you think through your systems of how robust a signal is, then ask yourself and know the answer in advance what data

would resolve the question. Yes or no, it does not really matter but you have to have that algorithm in place before you begin the system, not after you build it. Thank you.

Mark McClellan: Thank you, Mary. Okay, at this point, I want to thank all of you, especially our panelists, for getting this discussion off to a great start by emphasizing this is not the end, this is the beginning of a discussion. The breakout panels provide an opportunity for what the FDA would like to get in terms of much more detailed comment and input on these questions. The main questions are up on the screen behind me, but feel free to discuss or add any other topics or any other ideas that were brought out this morning or that you brought to the discussion yourself.

So just a reminder in terms of the logistics before everybody heads out, we are taking a break of about 40 minutes for lunch. If you ordered a box lunch online, you can pick it up outside the room. If you did not preorder, there are a few more available for purchase. There are restaurants in the hotel and in the area. The breakout sessions will begin at 12:45. Please be in your room listed on the back of your nametag at that time. If you registered onsite for some reason you were not assigned to a room, let them know at the desk and I think you can go to the room of your choice but we do want to have as much participation as possible in this next phase.

We would like for the breakout discussions to be concluded at about 1:45 or so and everyone back in this room at 2:00.

Thank you very much.

[Lunch Break - Disperse to breakout rooms]

Reconvene

Mark McClellan: Let me start this afternoon session with a special word of thanks. The first thanks go to all of you who stuck around for the day and contributed actively to your discussion sections. So I want to thank you for all the comments that you have made. By the way, if you could stop making the comments now so we can get on with the discussion that will be great, enough comments for the moment.

I would also like to give a special thanks to all the note takers in each of the 10 sessions. All of you who are facilitators should have or should be getting right now - this is real time you know - a typed up summary of the main points the note takers took away from your discussion. And looking at Richard's, it looks even very well organized, the bullets and everything, so that will hopefully facilitate this next session.

This is a report out of the breakout groups and as you all recall, there were four main questions that were used to get the discussion going. It does not mean that is the only thing

that people talked about or that people covered all of the questions.

I think the best way to do this is to just simply ask each of the facilitators to do a brief summary and if we keep it to several minutes, that will be great - a brief summary of their discussion. That may leave us a little bit of time after their summary presentations for further comments, questions and reactions in this larger group.

I know that you all have already put a lot of time and effort into this, but I do want to make clear that FDA is interested in getting additional comments. The docket for this meeting was opened with the Federal Register notice that appeared on December 5th and written comments can be sent to the docket even after this meeting. So with that, I would like to turn to our facilitators. Let me start with - again this is in no particular order but number one - Richard Platt.

Richard Platt: We had a terrific discussion. We were the group over here in case you saw a bunch of earnest folks and it was actually more that we talked about than we have time to discuss right now, so could we enter these comments in the docket, please? Okay, good. So then let me say I think we spent our largest amount of time talking about the vision thing and the three sort of high level thoughts about vision are ultimately, we want the system to help us identify risks from

drugs earlier and ascertain whether the signals represent real risks.

Second, that the initial version, what do we want in two years? It should be focused on specific use cases with an emphasis on quality of data, a solid understanding of data sources and less emphasis on quantity or number of lives covered, so if FDA has to make a trade-off, it should be on quality of data.

And finally, in governance at the highest level, we talked about who should have access to the system, and there was a very broad range of opinion, but there were several people in the group who thought of resources allowing everyone should have access. That this should be defined as much as possible as a public resource to which all comers would have some claim. It was appreciated that there are a million caveats around ensuring privacy and bandwidth and things like that but I think a substantial sentiment in that favor.

The second question around options for governance, a lot of good points were made with I think a preponderance of the view being that there should be some kind of sharing of governance. One model possibility to consider would be the U.S. Pharmacopeia Model, but the notion that there would be a number of stewards of the data would be something worth thinking about and still an appreciation that governance is too

complicated a concept to come up with one mechanism for it, and that there might be different aspects of governance dealing with conditions of participation or daily use or adjudication. There were a variety of pieces of Sentinel and each of them might be governed separately. There other great comments but why do I not hold off? If there is time for a second round, I'll add some more.

Mark McClellan: Okay. Thank you very much Rich. Number two is Shawn.

Shawn Murphy: Thanks, Mark. So we focused mostly on the first question, which was what is the vision for the nationwide safety network? Short term is one to two years, and long term is 10 or more years. And interestingly, it came clear that there are two dimensions that people wanted to talk about.

One was is this system going to be reactive or proactive? Now, I think we all have the idea that it is going to be both but reactive is that it is given a question and basically it is hypothesis testing; proactive being that it is active surveillance. And the second dimension was this distributed versus centralized system of querying and interestingly, centralized comes back out when you talk about national health networks and possibly using national health networks to perform this activity.

So in the one to two-year vision, I think that most of the consensus was to trade off and have relatively isolated centers that would be given a question specifically reacting to an issue that came up and that that center would then work with other centers to arrive at a determination as to whether this was a real signal or not, and that the focus then would be more on the development of these methods such that there would be communication and transparency between the teams that were working on the methods and on the question. And that much of what was being put into place would focus on making sure that agreement was on the methods and then a culture was developed such that working on questions such as this in a team at these various centers would be possible and productive.

In the 10-year vision, we got a number of very interesting views on this. I think that there clearly was the idea that proactive surveillance would be taking place and in that way, to enable that, you would either need a distributed system with very defined structures to data the way the data was being handled and so forth or that it would have to occur over a national health infrastructure of some sort. And the other thing to emphasize is that the two-year plan should actually evolve into the 10-year plan such that even though activities are occurring relatively isolated, there should be work towards normalizing data structures and codes and so forth such that

the 10-year plan would be realized since 10 years comes here before we know it, as we all know.

This idea of having some kind of prioritization [sounds like] committee that would then enable the network to be used for more than just pure FDA surveillance I think also came up on our team, and they thought that was important. And that finally, communication back through personal health records would be something that might be able to be realized, and that point of care modifications to systems such that better data collection would occur at the point of care or emphasis of what is valuable at the point of care would occur and EHRs and so forth would be enhanced in those manners.

Mark McClellan: Thanks very much for that summary, Shawn, and the next group number three - Marc.

Marc Boutin: Thank you. Group number three focused exclusively on governance. We found the topic difficult for one major reason, and that was we were looking at governance in the abstract rather than reacting to a proposed governance structure and that created some challenges for the group. We immediately identified a number of questions that included items like: Who will pay for it? Who will have access? Who will make the decisions?

The concept of looking at governance in the abstract I think was very, very difficult and what became clear was we

needed some sort of way to address the topic of governance in a way that would allow all the stakeholders to have some participation. And so the notion of an AHEC-like model was floated where there would be an advisory group of multiple stakeholders with subcommittees exploring the different topics of relevance. So issues like: How would you address methodologies? How might you address communications? How might you address the question of who has access to allow all the different stakeholder experts to have input and feed that up into a larger group that might then craft a very specific governance structure that could address some of the issues that all the groups had?

There seemed to be some initial debate on whether or not the governance would be a hybrid model or a fully-owned FDA model, and that seemed to quickly evolve to more of a debate over a hybrid with a spectrum of where FDA fell in terms of the amount of control it might have or oversight it might have over the governance structure.

There was also some discussion about looking at the governance issues from the bottom up in terms of resources. Who would do the work and how the aspects of this would evolve at the bottom level? But I think what came out of the group that was most compelling was there needed to be a structure to

involve all the stakeholders to make some meaningful recommendations in terms of governance.

Mark McClellan: Thanks very much for that summary, Marc. The next group is group number four - Marcy?

Marcy Wilder: Our group focused on the last two questions and not at all in the first two because we did not fall into that trap, which means we talked about risks and we talked about stakeholder input. It was a very lively discussion with lots of input and I think the most useful way to summarize what went on is to talk about what are some of the risks that were outlined and maybe some of the potential solutions.

The overriding concerns were one with false negatives and false positives from the system and all of the kinds of implications that it can have - everything from public misunderstanding of the safety signals. There was concern that there would be a proliferation of safety signals without any way to confirm them. There were the risks associated with overselling the program from the beginning. There was a great consciousness that we are at the very beginning. We are taking baby steps. We should not oversell. That we should, at least in the early stages, set this program up for success by carefully selecting the types of pilots and projects that we go forward and go public with.

There were concerns raised by some in the room about unfairness in the process and due process types of concern. So for example, there were device manufacturers that were concerned about visibility and access to the data used to make determinations. There was concern about who decides what questions will be asked, and that was related to concerns about how this program or this initiative will be funded. There was a little bit of concern about the one who pays the piper calls the tune. And so we looked at risks associated with a public-private funding mechanism and what are some safeguards and firewalls that can be put in place and process steps that can be put in place to guard against unfairness in that process and to ensure that public health -- that the overriding - if not exclusive, that the primary use of the system will be for public health and overriding public health concerns.

There was concern that there would be so much bureaucracy placed on the Sentinel Initiative that it would bog down and not be able to move forward. There was concern about insufficient resources. Not insufficient resources in the sense that the agency and others would need to fund not just a technical infrastructure but an administrative infrastructure that folks are going to need to be trained in the process and a structure put in place that lets scientists do the science and that it would be attractive to young scientists, that this

would be a happening initiative and public health would be happening once again.

In terms of the stakeholders, there were a number of different stakeholders that were raised. One of the ways to mitigate risks is to have an open and effective process where concerns are taken in and appropriately addressed and the different stakeholders - many of whom were represented in the room - were everyone, it was patients, governments, physicians, manufacturers, professional organizations, and hospitals. So there are many stakeholders in the discussion about how the FDA might go about getting appropriate stakeholder input. Folks went back to what they called the FDA tried and true. There are Federal Register notices. People were very clear that they wanted something in writing to respond to whether it was guidance that gets put out for public comment or just something maybe earlier or not quite ready for guidance but ideas put out on a website and enabling -- again, putting into writing and letting people respond.

There was a lot of talk about soliciting inputs from both patients and providers, the patient and provider communities, be it through town halls or blogs or YouTube and some of the other channels that FDA is using or starting to use. And there was also conversation about ROI and the fact that we are used to talking about ROI on infrastructure but we are not used to

talking about ROI, return on investment, for participation and that there is ROI from participation. And maybe if we could start measuring that somehow that would help us in thinking about what types of participation would be most valuable and most productive.

Mark McClellan: Great. Thanks very much, Marcy, and thanks to your group as well. Next up, number five, is Marcus.

Marcus Wilson: Our group focused primarily on question -- actually, totally on question three and in fact, we even got -- as we looked at risks, we only went to one dimension of risks and that tells you how deep the discussion was in the team and how involved everyone was around the table. The specific part about risk that we dealt with was around communication and I think many of us in the room feel that it is going to be the most difficult part of the Sentinel roadmap to fill out and it is going to take time to do that. And I think over time, this risk associated with communication will change and I think it will get much better. Certainly, early on, it is going to be tougher.

Marcy, I am going to try to add to some of the things you talked about. You mentioned a few things about false positives and false negatives and those are obvious areas of risk. And if you think about the time period we are most vulnerable to risks is at the time period where we generate a signal and we

are trying to determine if in fact it is real or not. And so that if all those are involved as we have thought this through, that is a big window of time when you do not know exactly what to communicate to whom and when to do that. So I think that is when we really need to get much more substance around.

But there is also as an interesting dimension added to this as well, and if you think about it, it is not just a matter of false positives and false negatives but even when you know for certain that there is a risk that exists, when we communicate that risk out to the population as a whole, especially if the recipient is being a patient who is taking the drug, they are getting the risk in isolation of the benefit and all of our decisions that are made in healthcare - risk-benefit decisions - not benefit and not risk, they are the combination of the two. So to be aware of that, be careful with it. The context in which we communicate these things often is as important as a certainty with which we do it.

The other comment that was made that I agree with, Sentinel does not fit all. Not all drugs, not all issues need be answered by the Sentinel System and I think that is very true early on. I think we have to be careful what we ask the system to do because it will do what we tell it to do and it may or may not be the right answer we get out of it.

In terms of when we communicate what to whom, there was a bit of discussion around that. To some, there is a sentiment in the room that patients can handle more than we think they can handle and that we should be more forthright in communication of signals early on. I think there is some level of truth to that. I think there is also some pushback in saying that; well, we have to be careful because it can be over-interpreted.

And Mark, the group that you represent had a lot of thoughts on that as well, but the targets of the communications need to be all decision makers not just the patient. Obviously, they are really an important part of this but the healthcare community as a whole, the physicians, organizations that put together medical policy, the regulators, obviously, are very critical users of all the information.

Over time, despite the fact that we criticize clinical trials, clinical trials have been well vetted and so the trust is there around clinical trials, certainly much more so than it is around the Sentinel type of work that we will be doing and over time, we have to build that trust around the Sentinel System to make sure that we are believed as well as clinical trials are often believed.

The other thing is when we go back to the issue of Sentinel does not fit all, I think everyone in the room pretty

much agreed with the concept that there are really three different types of categories. There is clinical trial data; there is observational or epidemiologic data - the type of things we are talking about with Sentinel. But there is also a third category that can drive off a lot of this as well that I will add into this and that is the prospective type studies that are registry type studies that we are even going to the point where you would do a prospective design that has randomization introduced into it but observational in the backend of that. And I think those types of designs are going to be needed to be tried and tested in order to answer some questions because we are not going to be able to answer all questions with one specific design.

The other thing we talked about was a -- a point was made earlier; we want to do this in combination with other FDA programs that are in place. And as we look at gathering information on risk, we use those same channels, if we can, around the Sentinel to communicate back down the findings from those projects as well and it is being one of the mechanisms for communicating. And I will stop at that.

Mark McClellan: Thanks very much, Marcus, great discussion. Next is group number six, Kristen Rosati.

Kristen Rosati: First of all, I want to apologize to my group because we had a very rich, very nuanced discussion and

my remarks certainly will not come close to capturing what our discussion was.

One area of interest where we overlapped with the two groups who also discussed risk - which just shows you how significant that is - is we spent a lot of time talking about the risks of signal detection and when the result is actionable both for false positives, false negatives, tease out the risks to patients for getting off drugs early, risks to companies for everyone getting off their drugs early.

And we also talked about the risk to the FDA approval process and perhaps public reaction forcing the FDA to be more conservative than necessary in their initial drug approval process, which of course is one of the reasons why the Sentinel System will be so useful.

We also talked about the liability risks coming out of the signal detection process. The liability potentially of the collaborating partners who are running the analysis to not reporting directly to their patients and to providers but waiting to report to the FDA and to their collaborating partners, and also potential risks of tort liability to the companies if they do decide to report directly to the patients and their companies. So there are a lot of very tricky liability issues to weigh in how this is structured.

And then finally, we spent a lot of time talking about the risks of inappropriate use of data. There is still some uncertainty in terms of what identifiers will be available to the broader collaborators and what information will stay within the data sources. And then to the extent that any individual data travels to the FDA or its collaborating partners, whether that will be available under FOIA which is a legal issue that we need to resolve. And then, also, the concerns with access to the contributors' proprietary data that may flow through the system. Thank you.

Oh, most importantly, we actually came up with some potential solutions.

Mark McClellan: Great. Do not leave those out.

Kristen Rosati: I almost forgot the most important part. We talked about the need for development of good rigorous best practices. It is very important in setting standards for the conduct of pharmacovigilance that these issues are handled very similarly, especially in terms of dealing with the liability risks to both patients and to companies.

We talked about the need for good governance reflecting a very wide range of stakeholders and then also good policies and remediation and enforcement at a very early stage to make sure that the public is assured that their privacy is going to be protected.

Mark McClellan: Great. Thanks very much for that summary, Kristen. Next is group number seven, Jeff Kelman.

Jeffrey Kelman: We also had a very lively discussion. We focused on number four and in fact, we could have gone on another hour but I will try to summarize. We addressed the two questions. First is who are the stakeholders and what are their prime interests? And the first stakeholders were clearly consumers and their interests are safety versus privacy. The question of whether this is going to limit them having access to care or coverage, over who is going to actually do the governance, and it was felt that consumer input was very important.

The question of trust of public versus private entities, particularly insurers versus drug manufacturers, is the question of consent. Do we need specific consent or blanket consent? Is it enough to get a blanket signed off on an insurance policy for drug data to be useful? And the big concern of data breach, which is always a concern here.

Among the providers is the question of whether this is going to restrict care options. What is their liability if a drug is proven risky retroactively or going forward? What about false positives? Is this going to limit unnecessary use of drugs until that is worked out? How do the results get

disseminated? Is this going to be an added burden on providers to find out what the results of Sentinel are?

And the access to data and who owns the data, especially data that comes from provider records. Manufacturers felt that they were positively interested in early safety warnings but cautious about sensitivity versus specificity issues. And coverage issues whether this was going to be used by third party payers to cover drugs.

The data aggregators - another stakeholder - were interested in level playing fields for standard security and confidentiality. Insurers clearly are interested in formularies, benefits, in cost and their specific liability if they covered a drug that has an adverse event proven by Sentinel.

The government - always the last in line - is interested in safety, cost and privacy. A question of whether this is going to move over into comparative effectiveness and data to inform policy going forward.

The second question we addressed was outreach and this is actually more difficult than I sort of imagined till the discussion went through. Consumers, once again, we cannot overemphasize the point of early engagement with consumers if this is going to work at all. I mean you can engage them through providers, through campaigns as part of public health

campaigns, through insurers, through patient groups, disease groups, online groups and consumer publications. And the key message is there are going to have to be things like empowerment and safety as the issue of the Sentinel project. These will have to be multi-cultural, multi-linguistic and appropriate educational level.

The providers also will need early engagement to the providers in the trenches. Journals are obvious but state medical societies, general medical societies, the guideline groups, online groups, public health clinics, mental health clinics, and insurers such as Medline articles. And the key message is that this is educational safety information not particularly limitation of care. It was felt that, in general, pharma would know these materials but in terms of level playing field, that small manufacturers had to be brought into large manufacturers and small manufacturers may feel themselves edged out by Sentinel.

We briefly talked about governance only to the point where that if you do not have early consumer involvement in governance, it will be too late later on. And there were three main risks: one was the obvious one of data breach; the second is limitation of expectations that this is not going to end all adverse drug events; and the risk of excluding the uninsured or

disease groups or patient groups that are not demographically represented in databases.

Mark McClellan: Great. Thanks very much Jeff. Next up is group number eight, Fran Cunningham.

Fran Cunningham: Thanks. We concentrated on question number four and we had a very in-depth conversation - I shall say - so we kind of focused on two major areas.

In looking at the stakeholders, I think the overarching information that was derived from our group was regardless of the stakeholder, a very good sound definition of the Sentinel System needs to be in place. So in order to have the buy-in across the board, more than what we have out there now has to be put into place.

Secondly, what will the Sentinel Initiative give in very descriptive forms and I guess information more than what is available now by the FDA? So what does the Sentinel System really offer? Where are their problems now, and where will it excel? And that in turn will determine how to get buy-in from different stakeholders. So those are two very large points that kept coming up over and over again.

When we looked at specific stakeholders, we looked at patients, providers, government agencies, corporations, manufacturers. And with the patient population specifically, what was of interest for buy-in? It was accuracy of data, data

privacy and security of course, ownership of the data, but more importantly - and I think this is a very interesting take - is does the patient have the ability to opt out, and how do you offer that patient that ability in this overarching system? And I had not really thought of that before.

Also, with buy-in from a patient standpoint, can the information that is obtained be adequately interpreted and then given back out to the patient population? So from a communication standpoint, we are looking at it but more importantly, what extra information is the patient getting from this system and how is it helping? I think that was pretty important as well.

One of the other factors is communication between the patient and the provider. Although there is buy-in from a patient standpoint, is there enough buy-in from a provider standpoint? Do they have the ability to interpret and convey specific information from this given initiative?

There were several other things from the patient standpoint too but I will move on to the next and that is the provider. From the provider standpoint - I guess also provider and perhaps other government agencies - one of the biggest things is, how is the information or the accountability that comes from this information, how is it out there? What are the needs that need to be conveyed in order for a buy-in from an

agency or provider to be taken? What is the huge advantage here?

When we look at the actual Sentinel Initiative and the stakeholders, one of the biggest things also is what is the focus again? Is it just going to be new entries into the market? Is it going to be patent utilization? What are some of the things that you can tell the stakeholders that they want to have the buy-in and what they see the advantage coming back out of?

From a manufacturing standpoint, one of the things that was brought up was that this is the first time that I guess actual product data is going to be taken out of the hands of the manufacturer from a monitoring or a tracking standpoint at any one fell swoop, and so that is something that needs to be constantly conveyed to the manufacturers so they still have some type of hand in it and the ability to evaluate which I think is interesting.

And let's see what else that is different than what someone else has said. I think one of the other largest things is what do we really envision the Sentinel System to look like and do? And that visibility should be so very well thought out and described early on across the board for all stakeholders in order to have buy-in. And so there are things that already exist in different groups. There are things that exist with

CDC and other areas that are already operational and are there certain things and other disciplines as well as other government agencies in the healthcare area, specifically CDC, that are already doing certain things that could be automatically translated into the Sentinel Initiative at this point in time. That is it.

Mark McClellan: Fran, thank you very much. Next up is group number nine, Garry Neil.

Garry Neil: Thanks, Mark. I will do my best to try to represent the highlights of what was a very engaged, very energetic group and also we were very well represented by people from all of the stakeholder groups. We were focused entirely on question two, but the many pages of notes that I have following the discussion indicate the depth of which we tried to get into this on governance.

Beginning with an understanding that we need to look at certain assumptions around governance and we would also need to really consider in-depth some of the issues that are going to have to be addressed by any governance model. And there was considerable reference made to other models of governance, which we might look at both in public sector healthcare but also outside the healthcare industry to look at models of governance. We can come back and discuss some of that.

What it boils down to as we have already heard discussions around where will the Sentinel network live. In other words, who will own it? Who will make the decisions around it? Who will pay for it? Who will do the work and who will have access? And of course, all of this was really debated in the context of the environment that we currently live in and the expectations of both the general public and patients as well as government and other stakeholders.

Again, there are many models of ownership that were discussed, and I think I should parenthetically say that there was an undercurrent of wanting to recognize that we needed an enlightened governance wherever it was and a competent governance that would recognize that what the Sentinel Network really can be or should be is a national treasure, really a national resource for the public good and for public health but also with the potential of creating significant innovation for the United States and in fact, the world.

So there were models discussed about government ownership and control maybe through the FDA or through some other agency, public-private partnerships and even a minority view, I would say, on a purely private ownership of the network being able to provide services back on a contracting basis to FDA. If I had to try to represent where I thought the majority of people were, that would be in the public-private partnership. And

several actually brought up the idea that that public-private partnership might be best addressed by the Reagan-Udall Foundation.

There was a need wherever it was governed though to identify agendas and conflicts of interest and to be able to manage those in a transparent way. When it comes to who pays for it, again, recognition that this is for the public good and an important resource, and so there were many who felt that government appropriations would be most appropriate for this. But again, looking at the amounts of money that might be required to really build this out, it seemed that it may be difficult that funding may not be adequate with those resources and that Congress had historically asked that infrastructure for such public utilities be built with private capitals subject to government regulation and government being an investor of last resort. So I think the group was somewhat divided looking at -- but likely will require both the public and private input.

There were some concerns on the payment side about the ability of smaller more innovative companies if companies are going to have to invest in this to have the wherewithal to be able to manage that. And also a concern about how we would manage older products for which there are not a lot of

champions right now. And so these will have to be addressed in whatever funding model comes up.

Some innovative suggestions were brought up though that we could look at. For example, the FAA and the Air Traffic Control System where there is a tax basically placed on travelers to be able to pay for this or other utility models that seem to have some merit and could be explored as a way of funding it.

As to who decides who has the power and governance, it always comes down to that. We really want to have people that know what they are doing and again respect the fact that they have such an important critical resource in their hands. And should there be controls over access to the data? I think the overwhelming consensus is yes, there should, to a certain extent in that following section 905 of the FDA Amendments Act that access really should be for public health uses, for bona fide public health uses. And that people that have access to the data should have that intent and should be qualified in some way to be able to manage data and know what they are looking at, but we did not really get into a more in-depth discussion about that.

There is the importance about transparency brought up and that when studies are being run, I think there was a pretty much overwhelming consensus in the group that we would use a

mechanism either using the clinicaltrials.gov mechanism that currently exists or a mechanism like that so that when questions are being asked, it would be generally known that such questions are being asked through a protocol and the nature of those questions.

The results - good, bad or ugly - would be disclosed, published in a peer-review journal, or disclosed on the Internet as they currently are for other clinical trials and that the data need to be further collected and aggregated. Standards need to be set perhaps by the governance model to facilitate collection of data and analysis of data.

So I think that is my attempt to try to capture a very complicated and lively discussion.

Mark McClellan: All right. Thank you very much Garry. And now, last but not the least, group number 10, Alec.

Alec Walker: Thank you, Mark. The impassioned discussions of group 10 focused on a sub-rubric of number two, governance, and we looked at access to the data. There was a consensus that the data should be available beyond the FDA. The FDA should have absolute priority in using the data but beyond that, there should be some mechanism that involved a review panel whose standards would revolve around quality of science and public health importance in considering applications to use the data. That all applications whether

accepted or not would be a matter of public record, and that those that were accepted would have with them an expectation of a return of results to the agency and public dissemination of the results in some form.

The prioritization beyond good science and public health importance, it seemed to the group, would put safety at the top of the list and especially if there were any limited resources. After that, with some discussion or some dissension, there was the notion that studies of benefit might be approvable within this and even a variety of other activities relating to help in drug utilization. There was a sense that there was a possibility for misuse of the data but rather than catalogue the ways the data could be misused, we felt that it was simply clear that the panel had to be alert to the possibility of malicious use of the data as well.

We also recognized that the panel approving uses of the data would have to take into consideration one very important stakeholder, which would be the data holders such that making sure that they were comfortable that the processes for approving data requests did not in some way endanger or jeopardize them.

Mark McClellan: Okay, Alec, thank you very much and again, my thanks to all 10 of the groups for what was clearly, as many of you said, very spirited and engaged discussion.

Well, FDA wanted some discussion of these four major topics of vision, of governance, of major risks, and the stakeholder engagement. I think you really got it.

Before opening this up to a broader discussion, let me turn again to some of the FDA leaders who are up here to see if there are any initial questions or comments on the group readouts.

Female Voice: No.

Mark McClellan: No? You guys said it all. Okay.

Janet Woodcock: I just want to thank everyone for the obvious intense engagement and thought that went into this. This is exactly what we needed. We needed to have this universe of things that we have to think about laid out for us, and I think you have done a great job and I look forward to further discussion.

Mark McClellan: And we have a little bit of time for that further discussion now. I know many of you tried to be very concise in your comments, so let me ask first if any of the presenters or other panelists have additions or further comments that they would like to make, especially after hearing what all the other groups discussed. I think you all did a nice job. It was not planned this way; we covered all four questions and had some pretty thorough discussion of each. I think if you put all 10 of the write-ups of these groups

together, you have a pretty comprehensive overview of all of the challenges and even a bit of a path forward for this program, but let me make sure that there are no more ideas or comments that could add to this. Rich?

Richard Platt: The one I forgot that many in our group subscribed to was the notion that the effort that is going to go into building Sentinel should be harmonized - bad term - should take advantage of other initiatives in building IT infrastructure in the U.S. This should not be done as a one-off and that deserves to be in the record.

Mark McClellan: Yes, Deven?

Deven McGraw: In terms of the public-private partnership and how the government gets to participate in that, I know as well as you do, Mark, and several others around the table that that is sometimes a very difficult question, and that the government's role in a private sector body can sometimes be limited by federal laws. So I would definitely encourage you as you are looking at shaping this to look at what the AHEC successor entity went through in trying to structure essentially a private entity with government having a strong role in it and the difficulties that ensued there that they are working through.

Mark McClellan: Any comments on specific recommendations for this particular type of application and how to get that right?

Deven McGraw: Well, you know I think it goes back to my earlier comment. I am not sure there is enough on the table other than I think the successor to AHEC is being built on a private financing model, which I know makes the consumer groups a bit nervous in terms of what the priorities will ultimately be for setting standards. And they are a voluntary body and that is in part one of the reasons why the government is able to participate because it is a voluntary standard setting body.

When you are talking about something like Sentinel where I think you want to put in - I hope - place some rules about how data can be accessed and used and how do you enforce that, that to me is not so much voluntary. It may not be an exact model but I know from my own perspective that I want the government to have a strong role here whether it all has to be within the FDA's privy or whether there is a way to build strong private sector participation, and I'm definitely open to trying to help shape that. I'm not sure that I have any specific recommendations. It is not one of those instances where you have, well, "No, we cannot ever go down that road," but I think it is complicated.

Question and Answer

Mark McClellan: Other comments? May I ask any comments from the broader participants, not just the people at the table? We covered everything? I'm sorry, here. If you could get up here -- to any microphone will do.

Lone Simonsen: Hi, my name is Lone Simonsen and I'm representing Surveillance Data Inc., one of those small companies that have all the data you might ever want to look at. I was just wondering if you would update us on what the situation is with the foundation and the funding behind this initiative and how that is moving forward.

Mark McClellan: The funding behind the Sentinel Initiative or --?

Lone Simonsen: The foundation and --

Mark McClellan: -- the Reagan-Udall Foundation?

Lone Simonsen: -- the ideas about how to get funding into this for public-private partnerships.

Mark McClellan: Well, that is part of the issues that this meeting was intended to discuss, which are among the questions of governance and infrastructure support: How is it overseen and how is it going to be financed? And there were some comments from some of the groups related to that. I know from sitting in on a bit of the discussions that there are some comments about that as well.

Do any of you here want to add to this question of financing for Sentinel? I do know that the FDA has some core funding but my impression from the outside is that that funding is not sufficient to cover the full cost of the infrastructure and analysis and answering all the kinds of questions that come up. And also, we have at least a history of a lot of postmarket studies being supported by the companies whose products are involved in the surveillance itself, so it is kind of the place where we are starting from. Are there any comments on this? Yes?

Cherif Benattia: Because we have time, I just would like to add one more point that I would like that we keep in mind is when the database will be rolled out, we are going to find maybe thousands of adverse events that have never been reported. The question is going to be what are we going to do with these events? Do we have to report them as industry? Does the FDA have to -- so just -- I do not think we have an answer today but I would like that we keep it in mind in the future and say what do we do with adverse events data that we will find in these databases?

Mark McClellan: We certainly had a lot of the discussions around the false positives and false negatives and how to both oversee those methods and communicate about that.

Janet Woodcock: Yes. Actually, I think you are asking a regulatory question. Of course, we would resolve that before we go forward on this. We understand what you are asking but FDA will be participating with this so we will address that issue.

Mark McClellan: Thank you.

Ed Bortnichak: Hi, my name is Ed Bortnichak from Merck. I just wanted to ask, I think, a follow up to the question that was just asked but we really did not hear an answer on. What is Reagan-Udall's role going to be with the follow-up on this? Do you have a statement that you could provide on what the specific role would be?

Mark McClellan: Well, I think Janet or Rachel may want to comment on this as well. As Janet mentioned in her opening slides, the Reagan-Udall Foundation is a vehicle for public-private collaboration in support of the FDA's mission, not around regulatory issues or around science and evidence and exactly the sort of thing that a lot of the Sentinel Network would have to deal with. So as far as the vehicle for some of the public-private collaboration of this activity, it could serve in that role and I think that is definitely an approach that is under consideration and we had some discussion about it today. Do you want to add to that?

Janet Woodcock: I'll add to it a little bit. What is attractive about -- if we were -- now, obviously, on the table have been multiple options that the panelists have discussed, including a strictly government run by contract type of option or public-private partnership. One of the things that will be attractive if we were to do a public-private partnership is to get to the issue that was raised just now.

It is similar to the foundation for NIH, for example, where we were able to do partnerships with the government. It participates more fully because that entity was established by Congress at the service of the NIH, for example, and therefore, the NIH participates very extensively in the FNIH activities although it is not exclusively NIH-driven. So that is certainly one of the options that we are exploring that would give us a lot of input and oversight -- give the FDA a major and central role that allow us to partner with other entities.

Rachel Behrman: Although what we are kicking around a little bit internally -- and this gets to the point Garry raised, if you think about -- and what I mean by that is something that to a certain extent, a little piece would be kept to ourselves because if you think about if we have a concern immediately postmarket, we are doing something that truly remains, if you will, confidential with a particular company. In the initial stages, that may not be something that

we could pose the same way we would expect another entity who is doing more research-related activities or is not the federal government to be much more transparent. There are things that we just cannot be transparent about so when -- we have taken into -- and someone else used this word without prompting from us, I think it was Fran, a hybrid model. We have been thinking a little bit about a hybrid model.

Mark McClellan: Other comments?

Richard A. Forshee: Hi, I'm Rich Forshee from FDA Center for Biologics Evaluation and Research and I would like to return to some of the risk communication questions from earlier this morning. I was wondering if there is any current plan to develop a risk communication research program in advance of getting some of these early signals so we can start our message development early on and evaluate how people are going to respond to different ways of handling those risk messages.

Mark McClellan: Well certainly, there were a lot of comments today about the importance of risk communication generally and the importance of risk communication around Sentinel-type observational signal data in particular. I do not know if you will want to add to that now.

Rachel Behrman: Yes, a little bit. I think one initial version of the question is, what are the five things you would do first, a sort of to do list? I think we heard loud and

clear today that one of the messages that we have to hone first is exactly what is Sentinel; what it is going to accomplish in the short term. In the long term, that is why we asked that. What does it add? But yes, clearly from the outset, we have recognized that risk communication is a critical piece. Whether or not we believe that multiple false positive signals really will or will not be generated, we do have to understand how to communicate in this environment. And we are not facing this alone, by the way. Clinicaltrials.gov obviously raises that question immediately so we are not the only ones struggling with it.

Janet Woodcock: In fact, the AERS System right now receives 450,000 reports every year and we put that database out eventually publicly and other folks are analyzing it so I would say it is not like this. I recognize that this activity may raise additional signals but it is not like we have a shortage of them right now. The agency has put together a risk communication advisory committee that has had several meetings and there is a cross-Center Working Group thinking about research agenda as well as other activities around FDA risk communication.

Rich Forshee: Thanks. I'm glad to hear you are thinking about this yourself. A lot of good work going on in that risk

communication area and I think it would be helpful to tap into it. I'm glad to hear you are doing that. Thanks.

Mark McClellan: Thank you. Go ahead.

Male Voice: Thank you, Mark. One comment, one question - the comment is basically this is very exciting, very productive discussions. We are really enjoying it. I came from the industry; my name is [indiscernible] from Novartis.

Actually, I also like to expand that the early comments a couple of people mentioned about the false positive, false negative. Personally, I do not believe the false negative really is the issue because Dr. Woodcock mentioned in the beginning remark this Sentinel method is an additional tool rather than replacing any other existing tools so an active finding does not preclude other investigations, other source of signal.

And also, another point I would really like to really get a clarification is the mechanism in terms of the operation. The queries will be sent from network to the data holders and the data holders will conduct an analysis and send it back to the network for interpretation and action taken. Can I clarify in terms of what is really the query definition? That the query is just look at the drug-event pairs or it is a more scientific question about investigation, a drug association to a particular safety concern.

If I can extend it to one more point, I made it to that comment at the team discussion prior to regrouping because this is so important to our nation in terms of probably how is patient safety. We need to elaborate all the expertise, the experiences from all sectors. Obviously, I came from the industry, working in the industry for 20 years and I know government, academic, any industry have expertise in conducting safety studies and identifying signals and identifying risk factors of any safety issue for risk minimizations. So we strongly believe that all the parties' participation and contribution would be very important for the success of this program including industry participation and contribution. Thank you.

Mark McClellan: Thank you. Joe?

Joseph Selby: This is just another item to add to the list of things to do first. It comes from the discussion within our group where there was some lack of clarity about what Sentinel ultimately would be, what version 1 of Sentinel would actually be.

There was lack of clarity as to whether Sentinel would actually require the transmission outside of source organizations of linkable or identifiable information. I think the risk that was mentioned there and that concerns me is that as we enthusiastically talk about the potential of Sentinel, we

fail to, at some point, just one point perhaps, mention in the same breath the attention to patient privacy. And I think we just need to have a very clear story of what that is and I would think, probably, it would be a story of not sending linkable or identifiable data out of the source organizations because we risk variable responses state by state so that we wind up with different privacy concerns across the country.

Mark McClellan: Thanks, Joe.

Male Voice: Maybe going back to the comment related to communication but out of my field, but it seems any time something that is a bit green field as this initiative is, we all have our view of what it might turn into and so, in keeping of the principle of do no harm, I think it is very fair to say the issues of communication to consumers and related to false positives and what might that do to a pharmaceutical company or a device manufacturer, what might that do to patient compliance with something that they otherwise ought to have -- because the thought that comes to mind is this is just another tool in the quiver and the responsibility that I think we would all have would remain the same to ensure that the communication does not go out, that there is a certainty level to the science and the conclusion being drawn that it does not rise to the point of being communicated.

Now, I bring that up because a lot of the airtime - I think a disproportioned amount of airtime today - has been given to the fact that we ought to be exceptionally transparent and reach out to consumers and everybody and so on and that is good because I think that has been the thesis. But at the same time, that we must have a balanced view to the fact that we have to be responsible with that and that outreach and communication may, in fact, not be, again, the same for all strata that have been identified in stakeholders, which is the same model we used for experimental design - our city [sounds like] trials, you know. When groups are getting together to figure out whether a drug is going to be approved or not, nobody knows that until that meeting is held so there may be something to be said that transparency is not a panacea. We have to be very responsible about transparency of this data.

Mark McClellan: Thank you very much and I think you are going to have the privilege of the last question.

John Michael O'Brien: Well, thank you very much, John Michael O'Brien of the College of Notre Dame School of Pharmacy. In addition to echoing the comments that we have heard thus far about risk communication, I just want to thank FDA, eHI and the Engelberg Center for continuing to involve the colleges of pharmacy, the practicing pharmacists, and their inter-professional colleagues in their education and continuing

education to prepare to answer some of these questions as well as provide the education whether it is something similar to the CMS provider network that worked in the launch of part D or the public-private cooperation to help that education. That would be fantastic, thank you.

Summary and Next Steps

Mark McClellan: Thanks for that comment. That is actually a nice one to wrap up on, it was not the plan but I do appreciate it, thank you.

And let me echo just in closing that, well, first of all, again, some housekeeping points. The transcript for this meeting, the written summaries or readouts from the breakout groups are all going to be available post this meeting, so if you want to take a further look at what has been discussed here, that will be available. The docket is open for further comments at the FDA. This will certainly not be the end of the discussion.

One theme that recurred through all of the different discussions around vision, around governance, around risks and potential benefits, around stakeholder engagement, around all these issues is that the Sentinel Initiative, the Sentinel Network, can be a very important development for better evidence and for better healthcare, but it is not easy. And I sure appreciate all of the time and effort and careful thought

that you all put in to helping FDA and all of us as collaborators in this effort to make this new program as successful as possible.

There is no substitute for discussion, for this kind of participation and exchange of ideas and experience. I'm sure it is going to continue as the Sentinel Initiative moves forward but this has been a very important step in helping to bring this vision into reality and so I would like to thank all of you who participated and especially all of the staff here who participated in organizing this meeting, so thank you all very much.

With that, I would also like to wish you all happy holidays and turn the microphone back over to Janet Woodcock for some closing comments.

Janet Woodcock: Okay, well I think I would simply like to thank all the participants. I would like to add to Mark's thanks. We have all received extremely valuable insights from all of you and I think we have exchanged views across sectors. It is true as several of the panels raised that we have not clarified the vision yet of exactly what the Sentinel Network might look like in two years and in five years or in 10 years.

What I heard was that is a good thing because we are giving everyone the opportunity to participate in crafting this vision, taking into account all the important considerations

that are very different from different points of view, but I think all come together to form something that we can all support. And that is really what we want to do, it is to craft something that we can come together; we can find common ground and support moving forward. Everyone can be comfortable that this is a public good that we are building.

I'm not going to go through everything that was just raised by all the panelists. I think these insights were outstanding and it was very interesting that each group had something very unique to contribute, so at the end of the day, we really have a very full exploration of the multidimensional issues that we are going to have to deal with as we craft this and make it a reality.

To one of the groups though, yes, we will be developing documents and we will be putting them out for public comment and that is how we are going to go about doing this. So we will, with this input and possibly more input over the next six months or whatever, we will be developing some written documents that will go through all these issues that have been raised. How do you deal with centralized versus distributed? How do we discuss the liability risks? What are we going to do about that? How do we deal with that for each one of the stakeholders that might be? What about individual consent versus blanket consent and how is that going to be handled by

any party who would join on to this and provide data? We will address each one of those issues in writing and make it available for input and comment in our usual FDA process.

So what I would like to do now is first of all, I would like to thank Melissa Robb, who is leading this initiative and is doing a terrific job in helping put together this meeting. I would like to thank Janet Marchibroda and eHealth for their input and help in getting this excellent meeting together. I would like to thank Mark McClellan and Brookings for really putting their shoulder to the wheel and getting this set up and also all our, of course, distinguished panelists who each one of you have added something very important to this. And finally, thank all of the attendees for sticking with us during this entire discussion and we look forward to more discussions with all of you. Thank you very much.

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[End of transcript]