

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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PUBLIC WORKSHOP

MAXIMIZING THE PUBLIC HEALTH BENEFIT OF
ADVERSE EVENT COLLECTION

THROUGHOUT THE PRODUCTIVE LIFE CYCLE

Tuesday, January 29, 2008

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The workshop convened at 8:30 a.m.

in the NIH Conference Center, Terrace Level,
5635 Fishers Lane, Rockville, MD, Solomon
Iyasu and Judy Staffa, co-leads, presiding.

PRESENT:

SOLOMON IYASU	FDA
JUDY STAFFA	FDA

LANA PAULS	FDA
GERALD DAL PAN	FDA

PANEL 1: KEY RESEARCH QUESTIONS

MARIETTA ANTHONY	CRITICAL PATH INSTITUTE
JASON BERG	CANADA

DAN BUDNITZ	CDC
VICTOR GOGOLAK	DRUGLOGIC
MICHAEL COHEN	ISMP
TRINKA COSTER	WRAIR
JOSEPH CRANSTON	AMA
RALPH EDWARDS	WHO
ALAN GOLDHAMMER	PhRMA

JUDY JONES	PERI
HENRI MANASSE	ASHP

PANEL 1 (continued)

SARA RADCLIFFE	BIO
JUNE RAINE	EMEA
BOB SHARRAR	MERCK

PAUL STANG	J&J
NOEL WATHION	EMEA

PANEL 2: RESEARCH APPROACH AND METHODS

ANNE TRONTELL	AHRQ
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FRAN CUNNINGHAM	VA
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WAJU DAI	SANOFI
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GRETCHEN DIEK	PFIZER
---------------	--------

RALPH EDWARDS	WHO
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VICTOR GOGOLAK	DRugLogic
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JIM KOTSANOS	LILLY
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JUDY KRAMER	Duke University
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GARY LACEY	Australia
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JOHN MCGLEW	ACCP
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RICHARD PLATT	Harvard University
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SIDNEY WOLFE	Public Citizen
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P R O C E E D I N G S

Time: 8:31 a.m.

DR. IYASU: Good morning. I am Solomon Iyasu. I am the Division Director for Epidemiology in the Office of Epidemiology of CDER.

I want to welcome you to this public workshop, which is entitled Maximizing the Public Health Benefit of Adverse Event Collection Throughout the Product Life Cycle.

I want to welcome you for this discussion, because I think this is an important initiative, and we are looking forward to your input on this subject area, which is very critical in terms of our post-marketing surveillance.

If we could go around the table, just to introduce briefly yourselves, where you come from, your name and your affiliation, I think it would be -- we will get started after that.

DR. DAL PAN: Good morning. I am

1 Gerald Dal Pan, Director of the Office of
2 Surveillance and Epidemiology at CDER at FDA.

3 DR. EDWARDS: Good morning. I am
4 Ralph Edwards, the Director of the WHO
5 Foundation Collaborating Center for
6 International Drug Monitoring, Uppsala,
7 Sweden, usually called the Uppsala Monitoring
8 Centre, for short.

9 DR. RAINE: Good morning. I am
10 June Raine from the European Medicines
11 Evaluation Agency in London, and it's a great
12 privilege to be here at this very important
13 and timely workshop.

14 DR. CRANSTON: Joe Cranston,
15 Director of Science Research and Technology at
16 the American Medical Association.

17 DR. BERG: Jason Berg. I'm the
18 Manager of Policy and Regulatory Affairs at
19 Health Canada. We are the Canadian regulator
20 of health products.

21 DR. WATHION: Good morning. My
22 name is Noel Wathion. I am the head of post-

1 authorization at the European Medicines Agency
2 in London.

3 DR. COSTER: I'm Trinka Coster.
4 I'm with the Army Surgeon General's Office.

5 DR. COHEN: Mike Cohen from the
6 Institute for Safe Medication Practices.

7 DR. BUDNITZ: I'm Dan Budnitz.
8 I'm from the Division of Health Care Quality
9 Promotion at CDC.

10 DR. SHARRAR: I'm Bob Sharrar.
11 I'm from Merck. I've been working in product
12 safety, primarily post-marketing surveillance,
13 for the last 17 years.

14 DR. MANASSE: Good morning. I'm
15 Henri Manasse. I'm the Chief Executive
16 Officer of the American Society of Health
17 System Pharmacists. We represent about 36,000
18 pharmacists practicing in hospitals across the
19 country.

20 DR. GOLDHAMMER: Alan Goldhammer,
21 Regulatory Affairs at PhRMA, and I think we
22 are reason for this meeting, because we

1 proposed this back about two years ago or year
2 and a half ago during the PDUFA discussions.

3 DR. PAULS: I'm Lana Pauls, the
4 Director of the Quality Management Staff in
5 the Center for Drugs.

6 DR. STAFFA: And I'm Judy Staffa.
7 I'm the Acting Associate Director for
8 Regulatory Research in the Office of
9 Surveillance and Epidemiology in Center for
10 Drugs at FDA.

11 DR. IYASU: Thank you all. Before
12 I introduce Dr. Gerald Dal Pan, I will ask
13 Lana Pauls to say a few words about logistics.

14 DR. PAULS: I am also the
15 logistical coordinator for today. So just for
16 those of you who are interested, there is
17 coffee and tea in the far back to the right,
18 and that will be available all day with a
19 couple of snacks.

20 The restrooms are out through
21 these glass doors to the left. There is
22 absolutely no cellphone and/or Blackberry

1 transmission downstairs on this level. So
2 during breaks, you need to go up to the first
3 level, and there is good reception up there.

4 In regard to the use of these
5 microphones, please make sure that you see the
6 red lights, because only six of them can be on
7 at one time. If you have any other questions
8 throughout the day, feel free to just grab me
9 at a break. Thank you.

10 DR. IYASU: Okay. Let me
11 introduce Dr. Gerald Dal Pan, who will give
12 actually the opening remarks today.

13 Dr. Gerald Dal Pan is the Office
14 Director for the Office of Surveillance and
15 Epidemiology at CDER.

16 DR. DAL PAN: Good morning. As
17 Solomon said, I am Gerald Dal Pan. Can you
18 hear me in the back? Okay. And I am the
19 Director of the Office of Surveillance and
20 Epidemiology, and our office is the office
21 that's principally responsible for review of
22 post-marketing adverse event information for

1 drugs and therapeutic biologics.

2 We are here today to discuss
3 approaches that FDA can take in developing a
4 procurement proposal to understand better the
5 public health value of spontaneous adverse
6 event data and how we can maximize the use of
7 these data.

8 This, as Alan mentioned, is one of
9 our commitments under PDUFA-4, and it is one
10 of many initiatives we have ongoing at FDA to
11 modernize the drug safety system. I'll name
12 a few others here.

13 One of them that I'm sure you have
14 heard about is an effort to increase our use
15 of population based data to perform
16 observational pharmaco-epidemiological
17 studies. We are also interested in using
18 large population databases to develop methods
19 for active surveillance.

20 So you might ask yourself why, if
21 we are interested in all these new initiatives
22 -- why are we so interested in spontaneous

adverse event data at the same time?

The simple answer is that the data from this system really has been the cornerstone of FDA's post-marketing drug safety efforts for the last 40 years or so, and they have been the basis for many important drug safety regulatory actions.

These data continue to be important, and indeed we are receiving increasing numbers of spontaneous adverse event reports each year.

So our spontaneous adverse report data are stored in a system called the Adverse Event Reporting System or AERS for short, and we thus call the data in the database AERS data, and that is a term you will probably hear throughout the day.

Now the basic strengths and limitations of AERS data are well known. AERS data are widely regarded as being useful for detecting relatively rare but serious events that are typically related to drug exposure

1 and otherwise have a low background frequency,
2 things such as Stevens Johnson Syndrome, acute
3 hepatic failure, certain blood dyscrasias.

4 By way of contrast, AERS data are
5 generally regarded as not being useful for
6 detecting increases in the frequency of
7 adverse events that are already common in the
8 population taking the medicine. So, for
9 example, AERS data are not very reliable in
10 detecting an increase in the frequency, say,
11 of heart attacks in patients with diabetes who
12 are taking a certain drug.

13 Other challenges with AERS, as you
14 will hear this morning, include a marked
15 underreporting of cases, variable quality of
16 the reports, and the presence of many factors
17 in the case narratives that can confound the
18 assessment of the relationship of the drug to
19 the adverse event.

20 So given what we know about the
21 strengths and limitations of the system, why
22 would we want to study the system itself at

1 this time? The truth is, we know very little
2 about the properties of this system.

3 There have been studies that have
4 shown the importance of these data in
5 identifying adverse events that have led to
6 either market withdrawal or the addition or
7 modification of a boxed warning to a product's
8 label. There are still a lot of unanswered
9 questions about the data, however.

10 For example, when in the life
11 cycle of a drug are the most clinically
12 important adverse events reported to FDA? Is
13 there a time after which there is no longer
14 any use to collecting spontaneous adverse
15 event data? What is the value of collecting
16 information on adverse events that are not
17 serious?

18 These issues have never been
19 systematically studied, and as FDA faces more
20 and increasingly complex drug safety
21 questions, answers to questions such as these
22 will be important, as they will help us to

1 maximize the use of AERS data.

2 Now maximizing the use of AERS
3 data will require careful consideration of
4 what questions we need to ask to understand
5 the system more fully, and what approaches we
6 need to take to answer these questions.

7 So toward this end, we will
8 issuing basically a request for a procurement
9 to accomplish this work. But before we can
10 prepare a procurement request, we have
11 organized today's public meeting in order to
12 obtain broad input on what the most relevant
13 questions are and what some possible
14 approaches to answering them could be.

15 So we will begin the day with
16 three -- with four presentations by FDA staff:
17 First, Min Chen, Associate Director in the
18 Division of Drug Risk Evaluation, will present
19 an overview of adverse event reporting in the
20 AERS system.

21 Next, Dr. Cindy Kortepeter, a
22 Safety Evaluator team leader in that division,

1 will explain in broad terms the approach that
2 our safety evaluators use in evaluating AERS
3 data.

4 Much of the information in these
5 two talks may be familiar to those of you who
6 work in this field. The purpose of these
7 talks is not to present a detailed overview of
8 all aspects of the AERS system and how FDA
9 evaluates the data. Rather, it is really to
10 set the stage for our panel discussion later
11 today.

12 After these two presentations, you
13 will hear from Mara McAdams, an epidemiology
14 and policy fellow in our office, who will
15 present the results of some preliminary work
16 she has conducted to examine the timing of
17 safety related actions throughout the life
18 cycle of new molecular entities approved
19 between 1991 and 2006.

20 Mara's research project is really
21 just a first look at post-approval safety
22 related actions. We are presenting it here

1 today not to discuss as a final or finished
2 piece of research, but rather to use it as a
3 springboard for further discussion of what
4 questions need to be answered.

5 At the end of these three
6 presentations, Dr. Solomon Iyasu, the
7 Director of our Epidemiology Division, will
8 summarize the issues that will be the focus of
9 today's discussion.

10 I will ask that you hold your
11 questions for the FDA presenters until the
12 first panel discussion, at which time they
13 will be able to answer clarifying questions.

14 Following the FDA presentations
15 and a short break, our first panel will focus
16 on the specific research questions to be
17 answered. An open public hearing will follow,
18 and after lunch our second panel will focus on
19 the research approach and methods that could
20 be undertaken. After a short break, there
21 will be another open public hearing, followed
22 by a wrap-up session.

1 I want to thank you all for coming
2 today, and I want to specially thank our
3 panelists who represent a variety of different
4 stakeholder groups and who will provide us
5 with a wealth of insight. So thank you all
6 for coming, and our first speaker will be Min
7 Chen, Associate Director in the Division of
8 Drug Risk Evaluation.

9 DR. CHEN: Good morning. Very
10 happy to be here and to give you an overview
11 of post-marketing safety reporting in the FDA,
12 specifically in CDER and CBER.

13 It was in 1962 that Food and Drug
14 and Cosmetic Act had an amendment called
15 Harrison-Kefauver Amendment, and that required
16 the approved applications from the
17 manufacturers, in addition to proof of
18 efficacy also required the company to send in
19 adverse event reports.

20 Over the years, there may be
21 changes of the regulations and guidances, but
22 currently these are the scope of the

1 regulations. For approved prescription drugs
2 under the New Drug Applications, abbreviated
3 New Drug Applications and biologic license
4 applications, all these are regulated under
5 the 21 CFR, it's called, Code of Federal
6 Regulations, 314.80.

7 For therapeutic biologics, there
8 are corresponding regulations, too. Generics
9 -- that was approved under ANDAs, also the
10 prescription drugs switched to OTC status and
11 the requirements are there. You have to
12 follow the approved prescription drugs.

13 For those products approved for
14 use prior to 1938, we call that grandfathered
15 drugs, have to follow 310.305, and only those
16 serious unlabeled event reports need to be
17 submitted to the agency.

18 For real over-the-counter drugs
19 that didn't have any approved applications,
20 we call that nonprescription over-the-counter
21 drugs. In the past there have been no
22 reporting requirement at all for adverse

1 events the manufacturer had received until
2 2007.

3 The FD&C Act, 21 USC 371, required
4 dietary supplements and over-the-counter drugs
5 submitting all these serious outcome reports
6 within 15 days.

7 For biologics in CBER, Center for
8 Biologic products, the human cells, tissues
9 and cellular and tissue based products,
10 including blood derivatives and vaccines --
11 they have similar regulations for safety
12 reporting.

13 In the 1990s internationally there
14 have been a lot of efforts through ICH or
15 International Conference on Harmonization that
16 developed many guidelines to support safety
17 reporting, related guidances, and FDA has
18 adopted quite a few of them.

19 For clinical trial safety data
20 collection, there are proposed expedited
21 reporting for serious outcome and causally
22 related event reports. That's called E-2(a).

1 For adverse event coding terminology, there
2 was a MedDRA developed called M-1. MedDRA is
3 Medical Dictionary for Regulatory Activities.

4 For electronic submissions, there
5 were E2B M2 developed. E2B is data element
6 specifications for individual safety reports.
7 M2 is for the electronic submission
8 transmission standard set up by these
9 guidelines.

10 Additionally, there is a periodic
11 safety update report guidelines developed
12 called PSUR under E2C.

13 Because of the international
14 development of the safety reporting, FDA about
15 four years ago developed a proposed safety
16 reporting rule, and the purpose, the rationale
17 behind it, is to codify all the ICH developed
18 -- the safety related guidelines. So,
19 hopefully, there is a global harmonization of
20 the safety reporting.

21 The goal is also to increase
22 quality of the reports by asking good

1 questions so we can acquire timely information
2 or complete information for serious outcome
3 reports.

4 Additionally, it includes
5 requirements for reporting medication error
6 related information. At that time, the
7 medication error was defined as any
8 preventable events that may cause or lead to
9 inappropriate medication use or patient harm
10 while the medication is in the control of the
11 health care professionals or consumers.

12 Finally, recently there is a --
13 There will be in the future an electronic
14 submission proposed rule coming out.

15 We have all these reporting
16 requirements for the companies to send in
17 reports. Also we have waivers. The scope of
18 the reporting waivers includes the following
19 two.

20 In 1997 and 2001 we published the
21 guidance asking the company to submit adverse
22 event reports that are both nonserious and

1 labeled events. That is reported, but the
2 reports have to be available upon FDA request.

3 The second one is the submission
4 of PSUR format. It is ICH format for the
5 currently required periodic adverse drug
6 experience report for CDER NDA products, ANDA
7 products, and for CBER products.

8 There are other waiver provisions
9 available, but it will be considered case by
10 case situation.

11 Where do we get all these reports?
12 the most majority of the reports we get are
13 spontaneous or voluntary from the public.
14 Once the company has received all these
15 reports, they are required to send the reports
16 -- turn around and send to the FDA directly.
17 Their report includes spontaneous source,
18 studies, clinical trials, any clinical trials,
19 domestic or foreign, any scientific literature
20 publications related to their product.
21 Foreign sources also include foreign
22 regulatory authority generated reports.

1 Here is a brief definition of
2 spontaneous reports. I think a lot of people
3 are very familiar with this. It is a
4 communication from an individual, either a
5 health care professional or consumer, to a
6 company or regulatory authority.

7 It described a suspected adverse
8 drug reaction in the patient or subject after
9 administration of one or more drug products.

10 This is a chart showing how safety
11 reports get to FDA. Patients, consumers and
12 health care professionals may send the reports
13 voluntarily to the FDA MedWatch website or to
14 the company, and then the company would turn
15 around and send to the FDA.

16 There are two types of
17 manufacturer's reports. One is called 15-day
18 or expedited alert reports. This includes
19 serious and unexpected or unlabeled events
20 that will be sent in expeditiously. These are
21 more important new information. We would like
22 to see them early.

1 The others are periodic reports in
2 the narrative summary format. These have to
3 be submitted quarterly for the first three
4 years after approval and annually thereafter.
5 This includes individual serious labeled and
6 all non-serious event reports. It has
7 descriptive or narrative summary and analysis
8 in this kind of format of the reports during
9 this period.

10 The reporting vehicle format in
11 the U.S. for paper reporting, we use 3500(a).
12 It is a mandatory form by the manufacturers.
13 If a foreign source reports, the companies can
14 use CIOMS 1 form.

15 For the public, they can use 3500
16 voluntary form. There is a health care
17 professional use of the voluntary form to
18 report anything related to the drug product
19 quality.

20 Electronic submission: Right now
21 we are using ICH E2B format through the FDA
22 gateway by the manufacturers.

1 Adverse event reporting system or
2 AERS -- I think everybody is also very
3 familiar with this. The data started in 1969.
4 However, the database was reengineered in 1997
5 to accommodate the ICH electronic submission
6 standards E2B and M2.

7 Currently, we would like to report
8 that there are more than 40 U.S. companies
9 participating in the electronic submission.
10 Just last year there were more than 70 percent
11 of the 15-day reports we have received via
12 electronic submission. This is very exciting.

13 There are some papers still sent
14 in to the FDA. The process of the paper
15 reporting is: We scan the reports first, and
16 we enter all the text in the reports into the
17 system manually. The adverse events, also the
18 indication use, if reported in the reports,
19 would be coded with MedDRA.

20 We get a lot of reports. However,
21 I would like to mention that the nonserious
22 outcome periodic reports after three years of

1 marketing are not entered into our system, due
2 to some limitations on resources.

3 This is a chart about how we get
4 the safety reports into AERS. From the
5 public, it is direct reporting using FDA 3500
6 form, and then the paper version will be
7 entered into AERS. From the industry,
8 manufacturers, we use ICH E2B electronic
9 submission or you could use paper form 3500-A
10 sent in.

11 Then once they are entered into
12 the system, we will do MedDRA coding QC for
13 the electronic reports. We also do MedDRA
14 coding by FDA manually for all the paper
15 reports.

16 This is a chart showing all the
17 reports that are entered into our database in
18 the last 11-12 years or so. You can tell that
19 the increasing trend of the reporting, and
20 that is a challenge for us, too, how to handle
21 these reports.

22 For the public, there are two ways

1 to get the AERS data. One is through the OSE
2 website. We have the quarterly data extracts
3 published on the website for people to
4 download at no cost. This includes
5 demographic information of each case, each
6 report we have received. Examples like drug
7 name, reaction or MedDRA term, outcome and
8 source reports.

9 It is also available through NTIS,
10 the National Technology Information Service.
11 You can request that online at a cost.
12 Individual case reports identified from this
13 listing of the information, you may request
14 these individual reports through FOI, Freedom
15 of Information staff in the FDA. However, the
16 patient and the reporter information -- they
17 are confidential. So they will be redacted
18 before releasing.

19 Finally, this is a summary of the
20 reports FDA receives or gets in AERS. For the
21 U.S. origin reports, we have direct reports,
22 including serious and nonserious outcome

1 reports for the lifetime of the product. If
2 the public reports, we will get that. We will
3 put them into the system.

4 From the manufacturers, there are
5 serious labeled and unlabeled, both of them,
6 required to be submitted to the FDA for the
7 lifetime of the product. However, for
8 nonserious, labeled or unlabeled, outcome
9 reports or periodic reports, after the first
10 three years of approval, we are not entering
11 them into AERS. So we are not seeing them all
12 the time.

13 For those nonserious labeled event
14 reports, we don't get that. We don't even
15 enter them. You don't even have to submit it
16 from the manufacturers, if you request a
17 waiver.

18 For foreign source reports,
19 manufacturers -- they have to send in serious
20 unlabeled event reports for the lifetime of
21 the product. For foreign source -- U.S. or
22 foreign source reports on literature

1 publication of your drug, only serious and
2 unlabeled event reports need to be submitted
3 for the lifetime of the product.

4 For serious unlabeled causally
5 related reports in studies, whether it is U.S.
6 or foreign source, those need to be submitted
7 for the lifetime of the product. This is what
8 we get in our system.

9 So what do we do with the reports?
10 Our colleague, Dr. Cindy Kortepeter will give
11 you an overview of this. Thank you.

12 DR. KORTEPETER: Okay. Good
13 morning. My name is Cindy Kortepeter, and I'm
14 a safety evaluator team leader in the Office
15 of Surveillance and Epidemiology, which is
16 also known as OSE.

17 The purpose of my talk is to
18 describe how we use spontaneous adverse event
19 reports for signal generation and signal
20 evaluation.

21 You've heard a little bit about
22 the adverse event reporting system, or AERS,

1 from the previous speaker. The spontaneous
2 adverse event reports that we receive are
3 entered into this computerized passive
4 surveillance database.

5 AERS is our tool for storing and
6 analyzing adverse event reports, and it
7 contains data on human drug as well as
8 therapeutic biologic agents. That dates back
9 to 1969, and as of this month we have hit the
10 4 million mark with the database now
11 containing greater than 4 million reports.

12 AERS does not contain adverse
13 event reports for vaccine products. Those
14 reports are housed in a separate database
15 known as VAERS.

16 There are two primary areas where
17 we use spontaneous reports. We use them in
18 signal detection, and we also use them in
19 adverse event characterization. I will begin
20 with the signal detection piece.

21 Safety evaluators are reviewers
22 within the Office of Surveillance and

1 Epidemiology who play a critical role in
2 signal detection. Many of the safety
3 evaluators have assigned therapeutic
4 categories of drugs, and they routinely
5 monitor the adverse event reports that they
6 receive in their AERS inbox.

7 The inboxes contain all serious
8 unlabeled reports, all direct reports, and
9 some periodic reports, including specific
10 reports of events that we have requested from
11 the sponsors for the purpose of enhanced
12 pharmacovigilance.

13 Safety evaluators can also review
14 periodic reports for signal detection, and
15 this would include the PADERS, which are the
16 traditional periodic reports known as the
17 Periodic Adverse Drug Experience Reports, or
18 the PSURs, which are the Periodic Safety
19 Update Reports.

20 Our main mission with regard to
21 reviewing AERS inbox reports as well as the
22 periodic reports is to identify and assess

1 previously unrecognized or unlabeled serious
2 adverse events.

3 We monitor the products throughout
4 their entire marketing life cycle, which is
5 also referred to as the post-marketing period,
6 and safety evaluators often collaborate with
7 other OSE colleagues, including our
8 epidemiologists, as well as with medical
9 officers in the Office of New Drugs, when
10 assessing the potential signals.

11 This is an example of what a
12 typical safety evaluator's inbox will look
13 like. The inbox is basically a line listing
14 of the suspect products as well as the
15 reported reactions.

16 The first step in signal detection
17 is for the safety evaluator to review and
18 analyze the reports to determine whether it is
19 serious or nonserious and to determine what
20 the outcome is, and whether the adverse event
21 is labeled or unlabeled and, if it is labeled,
22 does the current labeling reflect the nature,

1 specificity and the severity of the event. Is
2 further workup of this reported adverse event
3 necessary? And for any particular case, the
4 safety evaluator has the option of clicking on
5 this "More" button here to obtain additional
6 details and information on the case and any
7 reported narrative description.

8 The safety evaluators analyze the
9 spontaneous reports to determine the
10 relationship between the disease, the drug
11 exposure, and the reported adverse event. We
12 determine whether there is a temporal
13 relationship between drug initiation and onset
14 of the event.

15 We look to see if there is any
16 dechallenge or rechallenge data. A single
17 case with a positive re-challenge can be very
18 compelling.

19 We determine if other illnesses
20 are present and whether those disease states
21 have an association with the adverse event.
22 We screen for other drugs, dietary supplements

1 or herbal remedies that were taken at the same
2 time, and we evaluate whether signs or
3 symptoms of the adverse events were already
4 present prior to drug exposure.

5 We also evaluate whether the
6 adverse event is consistent with the
7 pharmacologic effects of the drug or whether
8 it is consistent with known effects of the
9 drug class.

10 We can look to see if there is
11 data from preclinical studies or clinical
12 trials that may support the potential signal.
13 We look for alternative explanations that may
14 have caused the reported adverse event, and we
15 also evaluate any medical histories and
16 laboratory findings.

17 We then determine if the report is
18 well documented and worth pursuing and, if
19 necessary, we will contact the reporter to
20 obtain follow-up information and additional
21 details.

22 To further evaluate the adverse

1 event, we can identify clinically relevant
2 case reports in the literature, and we can
3 also search the AERS database for other cases
4 of the reported event for that particular
5 product or we can search for cases of the
6 reported adverse event associated with other
7 agents in the same class or having the same or
8 similar pharmacologic property.

9 The safety evaluators can also
10 generate an AERS standard report for all
11 events reported for a particular product. For
12 example, if I wanted to know what the most
13 frequently reported adverse events were for
14 Drug X, I could generate the standard report
15 that contains all the preferred terms reported
16 for a particular product.

17 In order to understand the adverse
18 event profile of this product, I could review
19 the top terms in the standard report or, more
20 importantly, I can group the terms together.
21 In this particular case, I could group terms
22 like dry mouth together with constipation,

1 hallucinations, and urinary retention, and
2 know that this drug has adverse event profile
3 that reflects anticholinergic effects. So
4 those are the effects that I should be
5 monitoring for.

6 Another utility of this report is
7 to screen for medically important events.
8 Take Stevens Johnson Syndrome, for example.
9 I may only have one or two reports of a poorly
10 documented case of Stevens Johnson Syndrome.
11 So with only one or two reports, the preferred
12 term Stevens Johnson Syndrome would not fall -
13 - would not rise to the top of this list.
14 However, near the top of this list may be
15 other terms such as dermatitis or blister.

16 So putting that together with
17 Stevens Johnson Syndrome, it would indicate to
18 me that I may need to be hypervigilant of
19 serious skin reactions.

20 One of the other tools we can use
21 with the AERS data for signal generation is
22 data mining. We can systematically mine the

1 AERS data using mathematical tools to identify
2 higher than expected frequency of product/
3 event combinations.

4 What this does is it assists us in
5 prioritizing our work. Data mining is a tool
6 for hypothesis generation or support for
7 further work on a hypothesis. We use it to
8 supplement our AERS inbox review, not in place
9 of it.

10 Data mining does not replace the
11 expert clinical case review and interpretation
12 that our safety evaluators do, and we are
13 currently exploring different methodologies in
14 order to capitalize on the full capabilities
15 of this tool.

16 If data mining suggests a
17 potential signal, we would still need to
18 review the individual cases. The cases we
19 retrieve from AERS are only as good as the
20 quality of the spontaneous reports that are
21 entered into the system.

22 A good case report will have a

1 thorough description of the adverse events, a
2 list of the suspect as well as the concomitant
3 medications, including therapy dates or the
4 dates of administration and other details.

5 It should contain a description of
6 patient characteristics such as demographic
7 data, baseline medical conditions, comorbid
8 conditions, past medical history, family
9 history and other risk factors.

10 It should contain information on
11 the diagnosis and how the adverse event was
12 diagnosed. Was a biopsy done? Did a
13 specialist make the diagnosis? Is there
14 supporting laboratory data? And finally, is
15 there any dechallenge and, more importantly,
16 rechallenge data?

17 So what exactly is a safety
18 signal, and how do these spontaneously
19 reported adverse events rise to the level of
20 a safety signal?

21 A safety signal can be a new
22 unlabeled adverse event. However, it can also

1 be a labeled adverse event, if there appears
2 to be an increase in the severity, specificity
3 or frequency of the event. In this case,
4 since it is already labeled, we would need to
5 determine if it is adequately labeled and
6 whether more prominence in labeling is
7 warranted.

8 A safety signal can be a newly
9 recognize interaction between a drug and a
10 drug, a drug and a food, a drug and a dietary
11 supplement, or a drug and a laboratory test.
12 A safety signal can also be a newly identified
13 at risk population such as the elderly or
14 pediatric patients.

15 Finally, safety signals can also
16 arise from spontaneous reports of medication
17 errors attributed to confusion with product
18 names or confusion with labeling or packaging.

19 Safety signals can come from many
20 different sources. A safety question may
21 arise from a spontaneous report in an AERS
22 inbox or it may come from data mining results

1 or from a periodic safety report, to name a
2 few.

3 This takes us to the second part
4 of how we use spontaneous adverse event
5 reports, which is adverse event
6 characterization.

7 We do this by pulling together
8 related reports to formulate a case series.
9 Why do we do this? Because of the nature of
10 spontaneous reports, it is highly unlikely
11 that a single report will contain all the
12 elements necessary to evaluate the adverse
13 event.

14 A case series allows us to pull
15 the data so that we can gain some useful
16 information to characterize the event. when
17 developing a case series, we first need to
18 determine how focused the AERS search should
19 be. We can search the database at various
20 MedDRA hierarchical levels. That ranges from
21 the preferred term or PT level and up through
22 the SOC or the system organ class level.

1 The level or levels that we search
2 at depends on the adverse event that we are
3 trying to define. For example, if we are
4 trying to work up a syndrome with nonspecific
5 symptoms, we would likely use a broader search
6 strategy.

7 We can also use case definitions
8 or standard measure queries, or SMQs, for
9 certain adverse events to further refine the
10 case series. In addition, we can use other
11 sources such as case reports from the
12 literature to supplement the cases from AERS.

13 We look for trends and patterns in
14 our case series. Were there more reports in
15 the pediatric or elderly populations? What
16 about males versus females? Did the event
17 occur immediately after drug administration in
18 the majority of cases? Did it occur mostly
19 with high doses? How severe was the reaction,
20 and did most patients require treatment of
21 some sort or did the patients recover without
22 intervention and just drug discontinuation?

1 A case series can also help us
2 identify risk factors. Were the majority of
3 the patients diabetics, for example? A case
4 series can provide us with some very useful
5 information that can be incorporated into
6 labeling so that patients and prescribers can
7 get a better understanding of at risk
8 populations and circumstances that may affect
9 risk, such as the dose or concomitant
10 medications.

11 So we have gathered information
12 from individual case reports and pulled
13 information about the adverse events from our
14 case series, and by doing so we have
15 identified possible populations at risk and
16 possible risk factors.

17 We have also researched the
18 biological plausibility and the class effect.
19 What we can do next is put it into
20 perspective. Our epidemiologists can
21 calculate a reporting rate and compare that to
22 the estimated background rate of the

1 particular adverse event in the general
2 population.

3 We can also compare the adverse
4 event profile of similar products or products
5 in the same class during a similar marketing
6 period.

7 There are challenges in evaluating
8 case reports, whether it is a single case
9 report or cases from a case series. It is
10 difficult to attribute adverse events with
11 high background rates to a drug or a
12 therapeutic biologic agent.

13 Events with long latencies such as
14 cancer may not be easily attributed to drug
15 exposure. Cases are often confounded by other
16 possible etiologies, and there is often
17 absence of complete diagnostic information.

18 There are limitations to the
19 utility of the spontaneous reports entered
20 into AERS, such as duplicate reporting and
21 extensive underreporting. The quality of the
22 reports can vary, and they are often

1 incomplete.

2 There can be reporting biases, and
3 although we sometimes calculate reporting
4 rates and compare them to background rates,
5 the actual numerator, which is the number of
6 cases occurring in the population, and the
7 actual denominator, which is the number of
8 patients exposed to the drug, are both only
9 estimates.

10 There are, however, strengths to
11 the spontaneous reports that are entered into
12 the adverse event reporting system. It
13 includes reports for all drugs and therapeutic
14 biologic products marketed in the U.S. It is
15 a simple and fairly inexpensive reporting
16 system, and it detects events that are not
17 seen in clinical trial.

18 It is especially good for events
19 with rare background rates, and we can put
20 together case series evaluations to identify
21 trends, drug indications, at risk populations,
22 and other clinically significant emerging

1 safety concerns.

2 The reports in AERS reflect a
3 realistic setting, unlike the controlled
4 settings that we see with clinical trials. As
5 such, AERS contains reports representative of
6 diverse patient populations, including the
7 elderly, pediatric patients, women and
8 patients from different ethnic backgrounds,
9 pregnant patients and those with comorbid
10 conditions. The indications we see can be
11 labeled or off label uses.

12 We see adverse events that are
13 reported with chronic use, and we often get
14 complicated patients on numerous concomitant
15 medications with multiple comorbidities, thus
16 making the cases complicated and challenging
17 to interpret, but they are reflective of
18 realistic situations.

19 So I have taken you from
20 spontaneous reports to working up a potential
21 signal. Now what is the outcome of all this?

22 Well, if the signal is deemed to

1 be credible, then some of the regulatory
2 actions that can occur include, but are not
3 limited to, labeling changes, public
4 communications such as "Dear Health Care
5 Provider" letters, FDA Talk papers, press
6 releases, public health advisories or alerts,
7 and regular posting on the MedWatch website.
8 And although not regulatory, we also publish
9 in medical literature as an additional
10 mechanism to communicate.

11 Other regulatory actions can
12 include restricted use registries,
13 pharmacoepidemiology studies, various risk
14 management strategies, medication guides,
15 pharmacovigilance plans such as enhanced
16 surveillance, and last but not least,
17 occasionally market withdrawal.

18 This concludes my talk, and I
19 thank you for your attention. I will now pass
20 the baton on to my colleague, Mara McAdams,
21 who will describe some of the research that
22 she has done in this area.

1 DR. McADAMS: Okay. Good morning,
2 and thank you for attending this open public
3 meeting. I am Mara McAdams, and I am the
4 epidemiology and policy fellow with the Office
5 of Surveillance and Epidemiology.

6 I have conducted a preliminary
7 research study to understand how long we
8 continue to make safety related action for new
9 molecular entities. The project is not meant
10 to answer the questions that have been put
11 forth by the Federal Register, but rather this
12 research is an initial look at safety related
13 actions.

14 We know that safety related
15 information can lead to changes in the
16 professional label or marketing withdrawals,
17 which we will refer to as safety related
18 actions.

19 No published research has looked
20 at the timing of safety related actions other
21 than boxed warnings and withdrawals.
22 Therefore, it is unclear to us how long after

1 approval safety related actions will continue
2 to occur.

3 We have designed a study to
4 estimate the median time until the most recent
5 safety related action. Additionally, we would
6 like to begin to characterize the frequency
7 and types of safety related actions.

8 Throughout this presentation, I
9 will be using the term safety related actions.
10 This term refers to both safety related
11 marketing withdrawals and safety related
12 labeling changes.

13 A safety related labeling change
14 can include a change to or an addition of a
15 boxed warning, a warning, contraindications,
16 precautions or adverse reaction.

17 For our study, we did not consider
18 edits to the safety label, but additionally,
19 we did allow for safety related changes.
20 Additionally, all safety related labeling
21 changes were meant to convey new safety
22 information that was not previously listed in

1 the label.

2 To better understand the timing of
3 safety related actions, we studied new
4 molecular entities or NMEs that were approved
5 by FDA between 1991 and the end of 2006. We
6 used NMEs that were approved after 1991,
7 because this time period will best reflect the
8 current practices at FDA. Additionally, data
9 prior to 1991 would be difficult for us to
10 obtain.

11 The unit of study in our
12 population was drugs. So I will be referring
13 to the cohort, which will be a collection of
14 NMEs, not a collection of people.

15 Our study population did not
16 include biologics that were approved under a
17 BLA. We did, however, allow for NMEs to
18 switch from prescription drug use to over-the-
19 counter use during the course of our study.

20 We are studying the timing of
21 safety related actions. Therefore, we will
22 follow an NME until the endpoint of the most

1 recent safety related action. But why did we
2 choose to study the most recent safety related
3 action?

4 To understand how long we continue
5 to make safety related actions, we need to
6 focus on the most recent action and not the
7 first action. This endpoint was either a
8 safety related labeling change or a marketing
9 withdrawal. The endpoint was the date of the
10 approval of a letter that approved the
11 supplement referring to the most recent safety
12 related labeling change.

13 We found the data from the medical
14 product safety information or from internal
15 agency records. The date that the NME was no
16 longer available to patients was considered
17 the endpoint for marketing withdrawal.

18 We obtained a list of safety
19 related withdrawals from the 2005 CDER report
20 to the nation, and the dates of the
21 withdrawals from internal agency records. We
22 also searched internal records to find the

1 dates of safety related withdrawals that
2 occurred after the publication of the 2005
3 CDER report to the nation.

4 We used a survival analysis method
5 to account for the fact that each NME will
6 have different amounts of time on the market.
7 Some of the NMEs will have at least one safety
8 related action, while others will have none.

9 We stopped observing an NME for
10 safety related actions at one of two times,
11 either at the end of the study period or upon
12 discontinuation of marketing for reasons that
13 were not safety related.

14 If the NME was still marketed in
15 September of 2007 and did not have a safety
16 related action, we censored the NME at the
17 study end. Additionally, the grouped the NMEs
18 by approval period cohort, because we were
19 looking at the time until the most recent
20 safety related action.

21 The time until the most recent
22 safety related action is going to depend on

1 the amount of time that the NME is marketed.
2 Those NMEs that we observed early in the life
3 cycle will be different from those that we
4 observed after many years of marketing. To
5 minimize these differences, we have conducted
6 the analyses in four approval period cohorts,
7 and I will explain these cohorts now in more
8 detail.

9 We have grouped the NMEs by
10 approval date, and we have constructed four
11 separate approval cohorts. The first group of
12 NMEs were those that were approved between
13 1991 and the end of 2004. The second approval
14 cohort began in January of 1995 and ended at
15 the end of 1998. The third cohort began in
16 January of 1999 and ended in the end of 2002,
17 and the fourth and final cohort began in
18 January of 2003 and ended in December of 2006.

19 We followed all four -- or all
20 NMEs in the four cohorts, regardless of the
21 approval period cohort, for safety related
22 actions until August 31, 2007.

1 Now I will begin to present the
2 results from our primary study goal, which was
3 to estimate the time that we continue to make
4 safety related actions.

5 We identified 444 NMEs approved by
6 FDA between January of 1991 and December of
7 2006. Seventy-eight percent of these NMEs had
8 at least one safety related action during the
9 study. Thirteen, or three percent, of the
10 NMEs were withdrawn from marketing for safety
11 related reasons.

12 These are the characteristics of
13 the NMEs by approval period cohort. The
14 entire follow-up -- Over the entire follow-up,
15 88 percent of the NMEs in cohort 1 had a
16 safety related action; 84 in cohort 2; 82 in
17 cohort 3; and 50 percent of cohort 4 had at
18 least one safety related action.

19 Additionally, I would like to
20 point out that, although the number of NMEs
21 approved in each cohort differed, the
22 proportion of NMEs withdrawn from marketing

1 and discontinued for nonsafety related reasons
2 was not very different between the four
3 cohorts.

4 I would also note that there were
5 fewer NMEs with safety related actions in the
6 fourth approval period cohort, because this
7 group of NMEs was followed for less than four
8 and a half years.

9 For each approval cohort, we
10 plotted the number of years between approval
11 and the most recent safety related action.
12 Each cohort is a snapshot of the timing of the
13 most recent changes in the dynamic life cycle
14 of NME use.

15 Cohort 1 will represent NMEs
16 marketed for up to 16 years. Cohort 2 will
17 present NMEs marketed for up to 12 years.
18 Cohort 3 will represent NMEs marketed for up
19 to eight years, and cohort 4 will represent
20 NMEs marketed for less than five years.

21 We see that for each of the
22 cohorts, safety related actions will continue

1 to occur throughout the follow-up period in
2 which the NME is marketed.

3 I would like to note that at the
4 end of the follow-up for the second, third and
5 fourth approval period cohorts is less than
6 that of the first cohort.

7 We can see from this data that for
8 as long as each NME is followed, safety
9 related actions will continue to occur. We
10 have detected actions occurring through the
11 end of follow-up for our study.

12 The median time until the most
13 recent safety related action was 12.3 years
14 for NMEs in the first cohort, nine years for
15 those in the second, 5.6 for those in the
16 third, and three years for those in the fourth
17 cohort.

18 The maximum number of years until
19 the most recent safety related action depended
20 on the amount of time that an NME was
21 marketed. We see that the maximum length of
22 follow-up is less than one year different than

1 the time between the approval and the most
2 recent safety related action.

3 Additionally, we have conducted
4 two in depth reviews. One will look at the
5 safety related actions that occurred more than
6 13 years after approval. The other examined
7 the frequencies and characteristics of safety
8 related actions for those NMEs that were
9 approved in the recent cohorts.

10 I will not begin by addressing the
11 first in depth review. We examined NMEs in
12 the first cohort that had a safety related
13 action that occurred more than 13 years after
14 approval. We conducted an in depth review,
15 because it is often assumed that only minor
16 changes occur after many years of marketing.

17 We chose 13 years, because it was
18 the third quartile of time between approval
19 and the most recent safety related action. We
20 will now describe these characteristics of
21 safety related withdrawals and labeling
22 changes.

1 Twenty-seven percent of NMEs in
2 the first cohort had a safety related action
3 that occurred more than 13 years after
4 approval. From this data we see that changes
5 to or additions of a boxed warning occurred
6 more than 13 years after approval. The
7 majority of these changes occurred in the
8 warnings or the precaution section of the
9 label.

10 I would like to note, too, that
11 changes can occur to more than one section of
12 the label during one supplement.

13 Now I would like to focus on the
14 frequency and the characteristics of safety
15 related actions for those NMEs that were
16 approved after 2003.

17 We chose the most recent approval
18 period cohort to study, because the actions in
19 this period most accurately reflect the
20 current trends, and the data was easy to
21 attain.

22 First, we noted the frequency of

1 safety related actions by documenting the date
2 of each change. For this group, we were able
3 to capture all safety related actions that
4 occurred between approval and August 31, 2007.
5 Then we calculated the median time until the
6 first safety related action and, additionally,
7 we described where the change was made to the
8 professional label and the source of data that
9 led to the first safety related action.

10 I would like to point out at this
11 time that we are now switching gears. In our
12 in depth review, we are analyzing the time
13 until the first safety related action for this
14 group of NMEs.

15 As you saw in our preliminary
16 results, half of the NMEs approved in this
17 group had at least one safety related labeling
18 change, and none were withdrawn from the
19 market as of August 31, 2006.

20 Therefore -- sorry, 2007 -- since
21 there were no withdrawals in this period, I
22 will use the term safety related labeling

1 changes rather than safety related actions.

2 For these 44 NMEs, there were 99
3 supplements that were approved for a labeling
4 change. In the next few slides, I will be
5 going into more detail about the timing of the
6 99 safety related labeling changes.

7 The median time until the first
8 safety related change was 2.6 years, and this
9 is in contrast to the median time until the
10 most recent safety related labeling change,
11 which was three years for this approval period
12 cohort.

13 The two medians are different,
14 because there are more than one labeling
15 change that occurred for some of these NMEs.
16 Additionally, we conducted a qualitative
17 analysis of the source of data that led to
18 safety related labeling changes.

19 There was a wide array of signal
20 sources for the first safety related labeling
21 change. However, the most common sources of
22 data came from clinical trials, clinical

1 pharmacology studies, and spontaneous adverse
2 event reports.

3 For some of the NMEs, multiple
4 sources of data led to the first safety
5 related labeling change. When this occurred,
6 clinical trials could lead FDA to check the
7 adverse event reporting system for reports.
8 Additionally, adverse event reports could lead
9 FDA to reanalyze clinical data.

10 I have plotted the timing of all
11 safety related actions for the fourth approval
12 period cohort for those NMEs that had at least
13 one safety related action.

14 In this figure, each line will
15 represent an NME. For example, this NME had
16 two safety related labeling changes. The
17 timing of the first safety related labeling
18 change occurred more than a year and a half
19 after approval.

20 I will now plot the 99 safety
21 related labeling changes. This is the timing
22 of the first safety related labeling change,

1 the timing of the second, third, fourth,
2 fifth, sixth and seventh safety related
3 labeling change.

4 We see that the timing of the
5 first safety related labeling change does not
6 directly affect when the subsequent safety
7 related labeling changes will occur.

8 From that previous figure, I would
9 like to point out that 25 percent of NMEs
10 approved in the fourth approval cohort had
11 more than one safety related labeling change.
12 The maximum number of changes was seven for
13 one NME, and additionally, 13 NMEs, or 15
14 percent of this cohort, had at least one
15 safety related labeling change within the
16 first year after approval.

17 This concludes the results of my
18 preliminary research project.

19 The strengths of our study are as
20 follows. We have conducted a detailed
21 analysis of the timing of safety related
22 actions, which is a more formal analysis than

1 the previous study is. We have studied a wide
2 array of drug classes. We were able to
3 capture a snapshot of the safety related
4 actions during different time points
5 throughout the first years of NME marketing.

6 As FDA staff, we were able to
7 complete the study, because FDA maintains the
8 information needed to address both the timing
9 and source of information for these NMEs.

10 Like any study, there will be some
11 limitations to our work. This is a
12 preliminary look that was limited in both
13 scope and duration. We did not consider
14 factors that may contribute to safety related
15 actions nor did we study NMEs that were
16 approved prior to January 1, 1991.

17 Our work will not be reproducible
18 by researchers outside FDA. Our study
19 documented the most recent safety related
20 labeling change and not necessarily the most
21 clinically important safety related labeling
22 change.

1 We could not address the duration
2 of time in which safety related actions will
3 continue to occur if we only looked at the
4 clinically significant labeling changes.

5 Finally, our work may represent
6 secular trends in the way FDA reviews
7 supplement applications for labeling changes
8 or drug withdrawals.

9 We know that the timing of an
10 action will not necessarily reflect the timing
11 of the detection of a safety signal.

12 I would like to emphasize these
13 following points. We found that the majority
14 of NMEs approved after 1991 had at least one
15 safety related action. Additionally, safety
16 related actions such as labeling changes or
17 marketing withdrawals occurred throughout the
18 life cycle of NME use. We found no
19 identifiable end to these actions.

20 Even after 13 years of follow-up,
21 we identified NMEs with serious safety related
22 labeling changes, such as changes to or

1 additions of a boxed warning or warning.

2 Though we were able to draw
3 conclusions about the timing of safety related
4 actions for NMEs approved after 1991, there
5 are still some reaming questions that we have
6 not answered.

7 For example, we cannot speculate
8 about the generalizability of our results for
9 non-NMEs, for combination products and others.

10 Finally, we cannot draw
11 conclusions about the sources of data for all
12 safety related actions. Particularly, we
13 don't know the contribution of spontaneous
14 reports. We don't know whether spontaneous
15 reports will suggest safety concerns before
16 other sources of data or whether the
17 contribution of spontaneous reports will be
18 informative years after approval.

19 I hope that our research project
20 has been informative and that this will help
21 guide the formation of the RFP. I will be
22 glad to answer questions or take any comments

1 during the discussion section.

2 Thank you very much, and also
3 thank you to the three contributing co-
4 authors.

5 DR. IYASU: Good morning. I am
6 Solomon Iyasu, Director of the Division of
7 Epidemiology in the Office of Surveillance and
8 Epidemiology at CDER.

9 This morning you heard from
10 several FDA speakers. Min gave an overview of
11 the AERS system. Cindy discussed how FDA
12 staff evaluate reports to detect safety
13 signals and monitor drug safety, and finally
14 Mara presented the results of the analysis of
15 the timing of safety related actions for NMEs
16 that were approved between 1991 and 2006.

17 In the next 10 minutes or so, I
18 will try to put what you heard together and
19 define the task for today.

20 Safety information come from
21 various sources during the life cycle of
22 products. Among these sources are safety data

1 that come from clinical trials. These trials
2 include premarket studies that essentially
3 define the safety profile of products before
4 market approval.

5 Additional data may also come from
6 subsequent trials on approved drugs seeking
7 new or expanded indications. Furthermore, new
8 safety information may stem from meta analysis
9 of existing clinical trials.

10 Important safety information may
11 also come from clinical pharmacology studies,
12 post-marketing observation studies and
13 registries. Spontaneous adverse event report
14 which is the subject of today's public
15 workshop is another important source and has
16 served as the cornerstone of post-market
17 surveillance for drugs for many years.

18 Finally, active surveillance, not
19 yet a reality, has the potential to provide
20 important additional data as a complement to
21 the existing post-marketing passive
22 surveillance system for drug safety.

1 The focus for today is spontaneous
2 adverse event reporting, which constitutes our
3 passive surveillance system for drug safety.
4 Spontaneous reports have a unique contribution
5 in post-marketing safety surveillance,
6 especially in detecting rare, serious events,
7 as mentioned earlier by previous FDA speakers.

8 Additionally, these reports play
9 an important role in characterizing post-
10 market adverse event experience and events.
11 These contributions are possible, because of
12 some notable advantages of the spontaneous
13 reporting system.

14 The system receives reports for
15 all U.S. marketed products and also from large
16 patient populations exposed to this product
17 after market approval. Additionally, the
18 system includes reports stemming from wider
19 indications of use than those studied pre-
20 market.

21 Thus, these reports represent real
22 life use and spontaneous -- real life use and

1 experiences, including chronic use, use in
2 patients receiving concomitant medications and
3 use in patients with comorbidities and
4 complicated clinical conditions.

5 Designing and maintaining the
6 collection, reporting and evaluation of post-
7 marketing adverse event reports involves costs
8 and requires infrastructure in both the FDA
9 and the regulated industry.

10 There are also challenges, already
11 expressed by previous speakers, specifically
12 regarding the quantity, quality and
13 interpretation of spontaneous adverse reports.
14 However, there have been efforts to improve
15 underreporting and the quality of reporting by
16 health care professionals.

17 The task ahead -- The task for
18 today, as we begin to transform and modernize
19 the science of drug safety, this is the time
20 to start and scientifically evaluate the
21 public health impact of spontaneous adverse
22 event reports on patient safety.

1 Why do we need to do an assessment
2 at this time? The reason is what we know
3 about this subject have mostly been based on
4 anecdotal information and few published
5 studies and examples of high profile marketing
6 withdrawals or informal qualitative studies.

7 To date, there has not been a
8 systematic and comprehensive evaluation of
9 value and role of spontaneous reports in
10 patient safety. Therefore, a systematic
11 scientific assessment is needed and is timely,
12 given the ongoing efforts to revamp our drug
13 safety system.

14 In contemplating such a huge
15 effort, we are faced with many challenges.
16 Good data are required to comprehensively
17 answer all the key questions, but obtaining
18 these data are challenging for several
19 reasons.

20 There is a less than optimal
21 tracking of the decision making process and
22 the type and chronology of the emergence of

1 scientific evidence for the basis for safety
2 concern. Pertinent data may reside in
3 multiple places, both within companies and the
4 FDA.

5 Availability of access to these
6 data may further be complicated by
7 confidentiality concerns. This might, in
8 turn, impact the reproducibility of the
9 results of such an effort. But all is not
10 doom and gloom.

11 We have learned some lessons from
12 FDA's preliminary work presented by Mara.
13 Relevant information to conduct and evaluation
14 of the passive surveillance system is
15 available within FDA, but documents and
16 records, as expected, are not in one place and
17 not easily available or retrievable.

18 Obtaining all the critical needed
19 information requires considerable time spent
20 talking or interviewing individuals involved
21 in the review and decision making process, all
22 of which Mara had to do multiple times.

1 Even after that, establishing the
2 time sequence of first signal discovery,
3 analysis and regulatory action can be
4 difficult and extremely time consuming.

5 Just to summarize, the key lesson
6 from the preliminary work is that safety
7 related actions occur throughout the marketing
8 life cycle. The work looked at only NMEs
9 approved between 1991 and 2006, but this work
10 does not provide all the answers.

11 It raises questions for us to
12 tackle and suggests some avenues of inquiry to
13 consider. For example, is this true for all
14 drugs other than the studied NMEs? What is
15 the role of spontaneous reports at the initial
16 trigger for the safety concern? How about
17 their role as a primary basis for safety
18 related regulatory actions?

19 How about their contributory role
20 as additional source augmenting other streams
21 of data? Does the role of spontaneous reports
22 change over time? And finally, is there a

1 time frame associated with the impact of
2 spontaneous reports on regulatory actions?

3 With that in mind, let me now turn
4 to the six questions published in the Federal
5 Register.

6 The first question is: What is
7 the value to patient safety of collecting
8 adverse events through a passive surveillance
9 system over the marketed life cycle of a
10 product? And how are these data best used in
11 regulatory decision making?

12 Second question: How can safety
13 issue identification and subsequent regulatory
14 action be characterized in relation to time
15 elapsed following product approval? Is this
16 influenced by the type of regulatory action
17 and/or the nature of the safety signal?

18 The third question is: What is
19 the role of serious and non-serious outcome
20 reports in safety issue identification and
21 subsequent regulatory action? How does the
22 role of these reports change over the

1 product's marketed life?

2 The fourth question is: What is
3 the role of reports by health care
4 professionals and consumers in safety signal
5 detection?

6 The fifth question is: Are there
7 any types of adverse event reports that are
8 not helpful to safety signal detection?

9 The final question is: What do we
10 know about non-reported adverse events or
11 characteristics associated with non-reporting?

12 There are two panel discussions
13 today. Panel 1 is tasked with providing input
14 on the six questions in the Federal Register
15 that I just read, as well as suggesting any
16 additional questions that should be considered
17 to frame the questions.

18 We would like Panel 2 to provide
19 input on the research approach and methods,
20 including hypothesis, study design, data
21 sources, outcome measures, and analytic
22 methods.

1 The input from this public
2 workshop will be used to publish a request for
3 information or an RFI to determine the types
4 of outside organizations that would be
5 interested and have the capability to conduct
6 the research to be undertaken under this
7 initiative.

8 Following FDA's evaluation of the
9 responses to the RFI, the FDA will issue an
10 request for proposal.

11 Thank you for your attention.

12 Now if there are questions, we
13 have about 10 minutes, I think, for clarifying
14 questions.

15 DR. STAFFA: Before we do that,
16 I'm wondering if panel members that may have
17 entered late after we did the introductions
18 could just introduce themselves. Dr. Jones,
19 I'm looking at you.

20 DR. JONES: I am Judith Jones, and
21 I am here -- I wear several hats, as many
22 people know, but I am here representing

1 academia as President of Pharmaceutical
2 Education Research Institute, which is an
3 accredited institute that provides training,
4 and also I actually teach at University of
5 Michigan in areas of drug safety, and
6 parenthetically, I used to be here at FDA and
7 also do drug safety consulting.

8 DR. STANG: Fresh from a layover
9 in the Grosvenor tube stop, I'm Paul Stang.
10 I am from J&J.

11 DR. STAFFA: And I think you have
12 a seat over here. Thanks. Sara?

13 DR. RADCLIFFE: I am Sara
14 Radcliffe. I'm Vice President for Science and
15 Regulatory Affairs at the Biotechnology
16 Industry Organization.

17 DR. STAFFA: Since we have 10
18 minutes before our break, we can go ahead, if
19 folks have questions about any of the
20 presentations that were given this morning.
21 First, we will start with questions from the
22 panel, and then we will open it up to others.

1 Any questions from the panel,
2 anything that wasn't clear?

3 DR. JONES: Well, I really
4 appreciated Mara McAdams' study. I was
5 wondering if you had a chance to -- whether
6 there was enough data to parse it in any drug
7 categories or event categories in terms of
8 safety related things. Safety related things
9 are so broad, and I was wondering if there was
10 any opportunity to stratify that data.

11 DR. McADAMS: I think everyone can
12 hear me on this microphone.

13 Yes, that is something we would be
14 interested in doing. We had 444 NMEs total.
15 Seventy-eight percent had at least one action.
16 Because it was the most recent action, we
17 didn't really feel comfortable in parsing it
18 out into what the actions were, but we feel
19 like for the RFP this would be a great
20 opportunity, looking at all actions, then
21 parsing them into the different categories.

22 We did, however, look for the

1 first safety related labeling changes, but
2 that was a much smaller population of only 44
3 NMEs. So there was no possibility to group
4 them. Thank you.

5 DR. GOLDHAMMER: I think you can
6 stay up there. I think you are going to get
7 a number of questions.

8 DR. McADAMS: I do know that.

9 DR. GOLDHAMMER: Anyway, yes,
10 congratulations on, I think, starting what is
11 going to be some very important studies, and
12 I have a couple of questions here.

13 DR. McADAMS: Sure.

14 DR. GOLDHAMMER: Did you make any
15 attempt at all to look across the drugs for
16 patient exposure numbers?

17 DR. McADAMS: That would be a very
18 interesting component. At this point, because
19 we don't have drug use data that goes back to
20 1991 on the patient level, it would be only on
21 the prescription level, we did not look into
22 that.

1 DR. GOLDHAMMER: Okay. The second
2 question: I think we are well aware,
3 certainly, of some high profile class
4 labelings that have taken place over this
5 time, and I know that was one of the areas
6 that you pointed to a need for. So you really
7 didn't try to focus down on some of these
8 things which might have been classes and
9 suggested by one drug in a class but really
10 not having data from the other drug.

11 DR. McADAMS: Yes. That is
12 actually one of the big limitations to our
13 study. I think I noted that. This is
14 something for the RFP. We were not able to
15 delve into that much detail in this project.
16 It would, of course, be of interest, but
17 remembering also we were looking the most
18 recent safety related action for drugs within
19 a class -- so, for example, the statins.

20 It might have been a class label
21 that was the most recent for one of them but
22 not for the others. This would just take more

1 time and effort to go into that detail.

2 So, thank you, and I guess I will
3 just stay here, if there's any other
4 questions.

5 DR. RAINE: Thank you. And again,
6 congratulations on excellent presentations.
7 I have a question, I think, more for Cindy
8 Kortepeter, which is: Do you collect data on
9 your signal processes? Do you collect data on
10 numbers of signals and when they are detected,
11 when they are evaluated, and when they are
12 completed?

13 DR. KORTEPETER: I guess I'm a
14 little bit unclear on the question. What kind
15 of data are you thinking of, like what kind of
16 signals we have collected and have taken
17 action on?

18 DR. RAINE: Simple metrics, how
19 often you do signal detection, what types of
20 signals, numbers and so forth, in order for us
21 to get an understanding of the operation of
22 the system.

1 DR. KORTEPETER: Okay. Yes, we
2 currently don't have any systems. I think we
3 are thinking of putting some systems in place,
4 but we do have -- With our project management,
5 they sort of monitor the projects that we do.

6 We have gone from a couple of
7 different systems of monitoring what we do.
8 So we are currently putting together a new
9 system, but there is no continuity just yet.
10 But that would be, certainly, something good
11 for us to do.

12 DR. STANG: Could I just get some
13 insight on question, the word characteristics.
14 It is unclear to me if the intent here was to
15 refer to characteristics of the event or
16 characteristics of the potential reporter of
17 the event.

18 DR. STAFFA: I think it's safe to
19 assume it's probably both.

20 DR. MANASSE: There were several
21 of the presenters who talked a bit about the
22 difficulty in obtaining data from existing

1 databases within the agency.

2 Are these issues of electronic
3 incompatibilities or are there other issues
4 that prevent that kind of integration?

5 DR. IYASU: I think I mentioned a
6 little bit during my presentation about where
7 the data may reside, that may have led to
8 consideration for safety. Some of it may --
9 Some of the problem is that the data may not
10 be fully electronic sometimes. Some of it may
11 be residing in the document room in paper
12 form.

13 So you have to compile all the
14 information to be able to put together a
15 complete picture of what actually transpired,
16 you know, right from the beginning up to the
17 end in terms of the evaluative process.

18 So it is a logistical issue that
19 requires a lot of effort, not just looking at
20 documents or looking at electronic records,
21 but also institutional memory in terms of
22 people who have been involved in all those

1 processes.

2 DR. SHARRAR: I am Bob Sharrar
3 from Merck. I have a question for Mara.

4 Mara, your slide number 11 -- can
5 you project it, please?

6 DR. McADAMS: Yes, I'll be glad
7 to. One second.

8 DR. SHARRAR: I guess this is --
9 what? -- a histogram showing the number of
10 reports that occurred by time intervals since
11 the drug was placed on the market?

12 DR. McADAMS: Yes. It's a
13 frequency of the most recent safety related
14 actions by year since approval, starting from
15 zero, going to 16. They are all on the same
16 scale.

17 DR. SHARRAR: Because as I look at
18 it, it seems as if the safety issues are
19 occurring earlier when the drug is put on the
20 market, because the peak of the curve is
21 moving to the left. Is that correct or not
22 correct?

1 DR. McADAMS: Let me just explain.

2 It was shorter durations of follow-up, which
3 is why I have noted the follow-up up there.
4 I don't think I need to point that out. It's
5 pretty clear.

6 The NMEs that were in the fourth
7 cohort were only followed up for four -- for
8 at a maximum of 4.4 years. Therefore, what we
9 are seeing on this slide is that actions will
10 continue to occur throughout the period that
11 we are observing them.

12 So think of each of these as a
13 snapshot of different periods within the life
14 cycle of the NME use.

15 DR. SHARRAR: It appears to me as
16 if the signals are being detected earlier when
17 the drug is put on the market.

18 DR. McADAMS: Yes?

19 DR. DAL PAN: I think -- This is
20 one of the most challenging things to
21 understand about these graphs, is what we were
22 trying to do here is say how long in a drug's

1 life cycle do we still make safety related
2 label changes.

3 So what Mara had is she had 16
4 years worth of new molecular entities, and she
5 divided them into four groups of four years
6 each, and because of the varying time period,
7 what you see here is -- Another way to look at
8 this is just before the end of follow-up for
9 each of these four cohorts -- remember, they
10 were followed for different lengths of time --
11 you see a lot of labeling and other safety
12 related actions near the end of the follow-up

13 I think that's the way we are
14 reading this, not the beginning of this. If
15 you look at the fourth cohort on the bottom
16 right, it is in the beginning, because there
17 only is a beginning. There is no year five,
18 six, seven, eight there. We only have four
19 years of follow-up there, and that's where the
20 labeling changes occur. They can't occur to
21 the right of that. That's why the arrows drop
22 down there, to show that.

1 If you look at the first one,
2 though, you see a shift to the right, because
3 things are happening late in the post-approval
4 life of that drug. What these are, it's a
5 frequency of number of NMEs that had a safety
6 related action at that time period. So the X
7 axis is the year after approval. The Y axis
8 is the number of NMEs there.

9 So the way we are reading this is
10 they are all shifted to the right, meaning
11 that things are -- important things are
12 occurring for the duration of follow-up.
13 That's the way we read it.

14 DR. STAFFA: And the other thing
15 to add into that is that this is a graph of
16 just the most recent. So it's not all.

17 DR. GOGOLAK: I would wonder what
18 the curve would look like if we looked at it
19 from the first safety alert that's occurred.

20 DR. IYASU: I think that would be
21 an interesting question to look. We haven't
22 actually tackled that area. We just wanted to

1 provide a snapshot of what we can do within
2 that short time.

3 So this is just looking at recent,
4 and I think that is the key in terms of
5 looking at this graph, that we are looking at
6 the most recent. So it's not looking at the
7 secular trend per se about safety related
8 actions.

9 DR. STAFFA: We have time for just
10 a couple of other questions. Any other
11 questions from the panel before we break?
12 Dan?

13 DR. BUDNITZ: I just want to
14 congratulate Mara and the whole office on the
15 beginnings of some excellent work. There are
16 a number of places maybe to go next.

17 Can someone answer where folks in
18 the office or Mara think about going next in
19 terms of is it rating some level of clinical
20 importance of these actions or where do you
21 see the next steps might be?

22 DR. McADAMS: That will be

1 dependent on who is asking the question, what
2 the interest is. For, I think, this
3 presentation and about the utility of AERS, I
4 am going to actually go to my final slide.
5 Sorry. Bear with me for a second, and we will
6 talk about the remaining issues that have not
7 been and further questions for study.

8 There are so many factors that
9 will go into why an NME has -- is it really
10 the labeling change or is withdrawn from
11 market, as Min has pointed out.

12 I think the first thing we would
13 want to know is how do generics affect the
14 timing of these actions? Is new information
15 coming in from combination product approvals?
16 Whether our work will generalize to non-NME
17 drugs.

18 Additionally, the approval of new
19 formulations brings in new clinical data. Is
20 that affecting the research that will then
21 lead to new actions?

22 So I think we can actually just

1 start with NMEs and tease out more of the
2 sources of data. The other major point is to
3 look and see what is the source of information
4 that is leading to this labeling change.

5 When I started to look into the
6 fourth cohort, looking at the sources of the
7 first labeling change, we found that it often
8 isn't information coming from one source, and
9 it was difficult to tease out which source is
10 actually coming first. That's kind of part
11 and parcel to the way things are stored and
12 the information was collected.

13 I am also going to probably turn
14 this over to Solomon, Gerald or Judy to see
15 what their input is, but I will leave this up
16 there, so you can consider.

17 DR. IYASU: Just because there
18 isn't really much time, I think this is just,
19 as I said, a preliminary work, and I think one
20 of the things that we are looking for from the
21 panel is to help us frame these questions.
22 What will be the best way to approach the

1 public health question that we are trying to
2 address here, because we have -- All of us
3 have to wear the public health hat, our public
4 health hat, and see where that we would get
5 the most bang for the time that we spent in
6 looking at this issue.

7 So I am not going to be sort of
8 directing where we need to go right now, but
9 I think your collective is going to be very
10 important.

11 DR. STAFFA: We have time for just
12 a couple of questions. We'll take Dr. Edwards
13 and Dr. Racoosin, and then we will take a
14 break. Again, there will be more opportunity
15 for the panel to ask questions after the
16 break.

17 DR. EDWARDS: Once again, my
18 congratulations for this very nice start to
19 investigate a most important matter.

20 There are lots of questions that
21 one can ask, but this is specific. On slide
22 15 you've listed, Mara, the box warnings --

1 sorry, the types of labeling change, and I
2 wondered if you had, actually, looked at the
3 time to a particular type of labeling change.

4 DR. McADAMS: Into a boxed
5 warning?

6 DR. EDWARDS: Well, or to -- into
7 the different categories you have there.

8 DR. McADAMS: We did not do that,
9 because that work has been previously
10 published. There's a JAMA article, and there
11 is another article by Diane Wysowski of our
12 office who looked at both the timing of safety
13 related withdrawals in boxed warnings.

14 Actually, I'm sorry, I don't have
15 a copy of that on me today, but that is
16 publicly available. So that work that has
17 been previously done.

18 DR. STAFFA: And Judy?

19 DR. RACOOSIN: Generra Racoosin of
20 CDER's Safety Policy and Communications Staff.

21 I just wanted to respond to one of
22 the issues that came up with the panel. As

1 Mara pointed out, it took a lot of work to
2 track down the regulatory history of many of
3 these safety related actions, and I just want
4 to point out that a year ago CDER established
5 a tracking system for post-marketing safety
6 issues.

7 So starting in January of 2007 and
8 moving forward, we have a repository for
9 archiving the regulatory history of post-
10 marketing safety issues that are emerging.

11 So although it's been a rough road
12 trying to track down these issues over the
13 last 15 years, from a year ago and moving
14 forward we will have -- It will be much
15 easier, because we have things all archived
16 in a single location. So just wanted to make
17 you all aware of that.

18 DR. STAFFA: And thank you for
19 helping us to get to break on such a positive
20 note.

21 We will take about a 12 minute
22 break, and we will be back here about 10:15.

1 Remember, there's refreshments down the hall
2 to the left. The restrooms through the glass
3 doors and to the left.

4 (Whereupon, the foregoing matter
5 went off the record at 10:03 a.m. and went
6 back on the record at 10:17 a.m.)

7 DR. IYASU: All right. We are
8 just about ready to get started, if everybody
9 could have their seats in the back.

10 For the next hour or so, we have
11 assembled a panel discussion on -- focusing on
12 the six questions that were published in the
13 Federal register, which were also on my
14 slides.

15 The six questions the panelists
16 have and also the public in the back have also
17 the copies of the questions. So later on when
18 we ask for input in the open public hearing
19 section, they will be able to look at the same
20 questions.

21 So this panel -- What we are
22 trying to get from this part of the discussion

1 is really to focus on the six questions and
2 any additional questions that the panelists
3 consider to be important that we need to
4 consider in our efforts to write a request for
5 proposal in the future.

6 So this will be sort of an
7 opportunity to brainstorm and gather
8 information about what the key questions are.
9 I think we are looking at this as an important
10 public health activity to try to frame the
11 question, identify the key issues, and then in
12 the afternoon when we have the second panel,
13 which will focus on sort of the methodologies
14 and also focus on how to operationalize the
15 questions that come up from Panel 1 in terms
16 of a research endeavor to evaluate.

17 So this is really essentially a
18 public health evaluation effort. So I am --
19 Judy and I will be co-facilitating this
20 discussion. So let's start with the first
21 question, and I would ask the panelists to
22 identify themselves, and then we will get

1 underway.

2 DR. STAFFA: I would just like to
3 add something to Solomon's background. As you
4 saw Mara's talk this morning, it stimulates a
5 lot of questions, and the reason we invited
6 this panel here today is because we know you
7 are very good at coming up with the important
8 questions. But what we need to do is to try
9 to focus on which are the most important
10 questions that we would like to then contract
11 out and get answered.

12 So if you can really just focus --
13 Your public health focus for right now would
14 be perfect to think about what are the most
15 important things we need to know? Is Mara's
16 approach, you know, kind of -- If we assume
17 for a moment that this is a relevant approach
18 to this issue, what kinds of questions are
19 important if at the end of the day we want to
20 be able to say what is the public health value
21 of this particular intervention, the passive
22 reporting system?

1 DR. MANASSE: Judy, I wonder if we
2 might just take a step back and perhaps ask a
3 more philosophical question, which is: Do we
4 want to maintain a spontaneous reporting
5 system approach or should we more assertively
6 begin to discuss an active reporting system.

7 We all know what the defects are.
8 I think there's been further explication of
9 that this morning, and with more drugs, higher
10 utilization, increased information about the
11 genetic relationship and drug action on
12 metabolism, you can go down a whole series of
13 factors.

14 Should we really rethink whether
15 we want to maintain and put all our eggs in
16 the basket of spontaneous reporting?

17 DR. STAFFA: Actually, I can take
18 a first shot at just offering a position on
19 that. In our office, we tend to look at it as
20 I don't think spontaneous reporting was ever
21 designed to be the total sum of what
22 surveillance and safety should be.

1 So I guess the purpose of this is
2 we are all very interested in mounting new
3 efforts, new systems. Active surveillance
4 pilots and initiatives are already underway.

5 So I think that's a given, that
6 those new systems will come on board, but what
7 today's effort is about is to try to answer
8 exactly the question that you have proposed,
9 is to say at the end of the day what do we
10 gain from this, and is it anything? Is it
11 something? Is it everything?

12 I don't think it's nothing or
13 everything. It's probably something in
14 between. But I would suggest others might
15 have --

16 DR. EDWARDS: I always want to
17 start by thinking of spontaneous reports as
18 concerns that are expressed by patients about
19 their treatment, and I think every reliable
20 large corporation is concerned to get
21 information about where their products aren't
22 living up to expectations.

1 So I think there is a public
2 health need to do that anyway in terms of
3 public confidence and so on.

4 It leads me, though, to the second
5 point, that I think if you have those
6 concerns, whether they are expressed directly
7 from a consumer or via a health professional,
8 I think there is a need to see them in that
9 way.

10 For example, I had several times
11 that -- and we know there is a concentration
12 on new, unlabeled adverse reactions. But if
13 there is a continuous complaint from the
14 public from, say, dependence on
15 benzodiazepines, and the number of complaints
16 goes up, that actually means something. It's
17 a signal, even though we actually know about
18 the pharmacological reasons for that.

19 So I really want to start off
20 keeping us fairly broad about how we think
21 about the information that we get, and also it
22 follows on, but we will come back to it, I'm

1 sure, the kind of information we are asking
2 people to send in, and that I would be much
3 more interested to know something about the
4 circumstances of the use of those drugs, and
5 we have touched on that two or three times.

6 So that's my starting shot.

7 DR. CRANSTON: I think -- and I'm
8 a non-expert in pharmacovigilance, but I think
9 -- I'm Joe Cranston from the AMA. I think,
10 from the standpoint of physicians, you know,
11 this type of system is really useful in
12 generating signals of rare but serious adverse
13 events, and if there are other systems that
14 Henri knows of in terms of more active post-
15 market surveillance that could do that, then
16 maybe it is past its time.

17 I think the critical question for
18 physicians, however, is then what is used with
19 the data. You know, I can think of different
20 examples as to how the regulatory action
21 ultimately came out.

22 You know, things like

1 serevastatin, it was fairly quick, you know.

2 It had an increased instance of rhabdomyolysis
3 as compared to a whole bunch of other drugs
4 that worked real well, and it got taken off
5 the market.

6 Phenylpropanolamine took forever.

7 I mean, you know, they had to do this very
8 fancy study up at Yale to finally show it
9 increased hemorrhagic strokes, and there is
10 still a debate as to whether your regulatory
11 decision on the SSRIs was correct.

12 So I think from the physician's
13 perspective, one -- right now, it's probably
14 the best system to identify rare but serious
15 adverse events that are not currently on the
16 label, and the critical question is, you know,
17 how valid is the data when the regulatory
18 action is taken.

19 DR. STAFFA: Since we are
20 transcribing the results from today so we can
21 take it back to the cave and actually look at
22 it, I'll ask you to just identify yourself

1 before your remarks so it's clear to us who
2 said what.

3 DR. RADCLIFFE: Sara Radcliffe
4 with the Biotechnology Industry Organization.

5 The answer to the question of
6 whether we should be moving to a more active
7 system is, yes. But that being said, it is
8 clear that there is still some value to the
9 passive spontaneous reporting system, and that
10 value is typically for particular types of
11 situations, situations where the clinical
12 event is distinctive and it is well defined,
13 where the background event -- where the
14 background rate is low, and so on.

15 I think that's probably familiar
16 to everybody on this panel. So there is a
17 value in specific situations, and I think the
18 difficulty is to reshape the adverse event
19 reporting system so that we can focus where
20 the value is the greatest.

21 So for example, as a number of
22 specific research proposals -- Before I came

1 here today, we reached out to BIO members, and
2 we asked them for information on specific
3 research questions that they would like to see
4 asked.

5 We got extensive input, and will
6 provide more detailed input in our written
7 comments, but just as a sort of a quick
8 overview, I think the kinds of questions that
9 came out were, for example, can we identify
10 those specific types of safety issues where
11 adverse event reporting is most valuable?

12 I don't know what those specific
13 safety issues are, but is there any way to do
14 that?

15 Is there a way to identify which
16 sources of adverse event reports tend to
17 produce the most useful and meaningful
18 information? So whether that's types of
19 practitioners or types of settings or whatever
20 it may be.

21 Finally, of course, the quality
22 versus quantity situation. I think most

1 people agree, we don't need more adverse event
2 reporting. We need better adverse event
3 reporting.

4 So how do you -- or can you
5 develop a system that helps to put some sort
6 of hierarchical priority on adverse event
7 reports so that the ones that are more
8 comprehensive or of higher quality are
9 weighted more than others? How do we do that
10 or how do we do that better?

11 DR. STAFFA: I am going to try to
12 go back and forth, so I'm equitable. Yes?

13 DR. WATHION: This is Noel Wathion
14 from the EMEA. I want to come back to the
15 philosophical question which was put, because
16 that was confronted, the same question, in the
17 European Union a couple of years ago after the
18 withdrawal of some high profile medicines.

19 What we decided at that particular
20 moment, all the regulating authorities, that
21 yes, it is needed; we should still maintain
22 it. And we don't call it a passive

1 surveillance system. We rather talk about
2 spontaneous reporting. It's a perception, you
3 know.

4 We said it's still a cornerstone,
5 and I think the strengths and the weaknesses
6 have been highlighted in the presentations
7 before the coffee break, but we have to
8 complement it with active surveillance, active
9 surveillance methods.

10 That led to the development of the
11 European risk management strategy. We are
12 just now going into its next phase. But you
13 also have to look back and say what can we do
14 better with it, because a number of issues
15 have been raised.

16 You have to be aware of the fact
17 that there are a lot of products on the market
18 which are OTC medicines for which you don't
19 have the health care professionals
20 intervening. So it is important that you try
21 to engage the patients who, in fact, are
22 moving from a more reactive consumer of health

1 care into a much more proactive behavior that
2 you can engage them.

3 That is why currently there are
4 legislative proposals in the EU talking about
5 patients reporting and what we can do. But
6 also how can we stimulate health care
7 professionals much better than they currently
8 are doing and making it a legal obligation to
9 be the answer to this, I think.

10 What can you do? What kind of
11 incentives can you provide? I think research
12 is further necessary, and I think Mara's
13 presentation, I think, was a very excellent
14 start in order to see what questions can be
15 raised.

16 Finally, there is a little nuance
17 in the EU and in the U.S. about what you are
18 looking into. We talk about adverse drug
19 reactions. We don't talk about adverse
20 events, because our legislation requires that
21 there is a reasonable possibility of a causal
22 relationship between the response and the

1 medicinal product. We don't know if it's
2 going to make such a big difference at the end
3 of the day, but there is a little nuance
4 between the two.

5 DR. STAFFA: Thank you. Alan?

6 DR. GOLDHAMMER: I think, too, the
7 philosophical question is an interesting one,
8 and I think all the parties are working to
9 resolve that with a variety of projects. FDA
10 has got projects going on. PhRMA has got
11 projects going on to see if we can come up
12 with some better ways to do proactive
13 pharmacovigilance.

14 I think, though, turning the
15 question back to the topic at hand here, I
16 think, is important, because a lot of people
17 are spending a lot of money on looking at
18 spontaneous reports, and when we first raised
19 this, we had a lot of anecdotal evidence that
20 companies late in the life cycle (a) weren't
21 getting much in, or there was very little in
22 terms of regulatory decision making that was

1 taking place because of spontaneous reports.

2 I think that the data that we had
3 from Mara is a real good start at this, but
4 unfortunately, there's an awful lot of
5 questions.

6 If we just look at the question
7 number 1 that was posed here, you know, we saw
8 decisions being made, what we would call
9 probably, late in the life cycle, certainly in
10 cohort number 1. But what we don't know is
11 how many of those decisions came from
12 spontaneous reports versus other data.

13 I would probably be willing to be
14 there was a fair number of that that was
15 probably class action -- class action -- from
16 class action law suits. But excuse me for
17 that Freudian slip -- but class effects that
18 maybe came from clinical trial data from drugs
19 that were subsequently approved, and then
20 there was a relook back at those classes of
21 drugs in that first cohort.

22 It would be very important, I

1 think, if we are trying to delve down into
2 this, is to sort the percentage of label
3 changes and regulatory actions that were
4 really a result of spontaneous reports coming
5 into the agency, because our intuitive
6 thinking when we raised this a year and a half
7 ago was that probably very few of them were.

8 So we need to build upon that
9 research, I think, with some more focused
10 questions.

11 DR. STAFF: Judith?

12 DR. JONES: Judith Jones, PERI. I
13 would like to just address two issues.

14 One is the value of the system is
15 not realized entirely, because the reporters
16 generally don't know much about the system,
17 and I think the meeting of this type and the
18 publicity around it is very helpful.

19 Very few medical schools -- I
20 think almost none now -- teach anything to
21 physicians about spontaneous reporting. And
22 one of the ways to achieve the kind of reports

1 that we just heard about, the high quality
2 reports, is just to make that part and parcel
3 of medical school teaching.

4 The second part -- I was very
5 pleased to see Cindy present some of the later
6 tools to support early decision making on a
7 single signal and augment that with,
8 obviously, your database.

9 I would go further to say that I
10 think there are -- that the key to the value
11 of this will be in the decision making process
12 and additional tools, most importantly, an
13 understanding of the population exposed at all
14 times.

15 That provides you a dynamic
16 denominator and allows the person viewing the
17 single and the multiple events in a very
18 focused way, and I think that can speed up the
19 decision making process sometimes.

20 DR. STAFFA: Thanks. Back to this
21 side. Michael?

22 DR. COHEN: I have a question and

1 a comment -- a point at least.

2 DR. STAFFA: Can you just preface
3 your comments with just stating your name?

4 DR. COHEN: Oh, sure. Michael
5 Cohen from ISMP. I'm sorry.

6 The question has to do with this
7 800 number that is being required now with
8 prescription drug dispensing, whether it's on
9 the container or whatever, and what impact
10 that might have or what your expectations are,
11 how that will be handled. Will that impact
12 our discussion today, as a matter of fact? I
13 think it might.

14 So I would like to hear from FDA
15 where that is going.

16 Then my comment is related to the
17 spontaneous reporting and maximizing the
18 public health benefit. I think one of the
19 things that we tend to do, I guess, is be more
20 concerned about that than we are about
21 communicating information back to the
22 practitioners.

1 I think, you know, I don't know
2 that MedWatch, for example, does the best job
3 in the world at communicating information back
4 out about specific issues. I think a good
5 research question would be how can you
6 maximize communication efforts about
7 individual drug related issues, adverse drug
8 related issues, including, of course,
9 medication errors, which is my area of
10 specialty.

11 I can tell you that, even with one
12 or two reports -- You don't need a lot of
13 data, but with one or two reports you can
14 identify some very serious problems that need
15 to be communicated immediately.

16 That may mean that you need to
17 work more closely with outside organizations
18 to turn that information around, and I think
19 that is an important public health benefit
20 that could be had from spontaneous reporting
21 that isn't right now.

22 Anyway, back to that 800 number.

1 DR. DAL PAN: So with regard to
2 the toll-free number on the packaging, we'll
3 have to see what the effect of that is. We
4 will certainly get more reports from it.
5 Whether we will get reports that have
6 sufficient amount of information to be useful
7 for the kind of inquiry we do with them
8 remains to be seen.

9 DR. STANG: Paul Stang, J&J. If I
10 can just pick up on a couple of the themes
11 that we have already heard, there have been
12 some research attempts to understand what does
13 motivate people to report, who the reporters
14 are, how much awareness they even have of the
15 system.

16 I think it has been shown in the
17 studies I have seen, some unpublished, that
18 physicians are the least informed, pharmacists
19 the most informed.

20 I wonder, inasmuch as we should be
21 including this in medical curricula, PAs and
22 nurse practitioners, pharmacists also have the

1 ability to cross over quite a bit of the
2 problems; and the main issues I have heard
3 back from some of the surveys that I have been
4 involved with is exactly to your point,
5 Michael.

6 People feel that when they report
7 these, it goes into a black box, and a lot of
8 the primary care guys that I have worked with
9 have said, if someone would just tell me if
10 they have ever had another report like this,
11 that's useful information to me.

12 So I agree. The idea of -- I was
13 hearing you say communication in a bigger
14 sense. I'm thinking of more immediate kind of
15 feedback to the reporter, I think, would be
16 interesting.

17 The other point I would ask is, in
18 the sense of the research that was presented,
19 if there is any way to tease out how much of
20 the motivation for the changes were actually
21 coming from the companies as opposed to coming
22 from the agency itself, because I think in the

1 last five years or so a lot of companies have
2 instituted fairly aggressive, robust systems,
3 and there have also been additional documents
4 that have been put in place. And what you may
5 be seeing or would be interesting to see is
6 how much of that change is actually coming not
7 from the agency necessarily but from the
8 industry itself.

9 DR. STAFFA: Which, I think,
10 underlies the importance of, if you are
11 gathering the data to address these questions,
12 you need to be prowling around in industry
13 files as well as FDA files. I think you need
14 both.

15 Back to this side. Yes?

16 DR. SHARRAR: Bob Sharrar from
17 Merck. I think that active surveillance will
18 never replace the post-marketing surveillance
19 system. I think that is a very important
20 point that hasn't been made yet. I think
21 Ralph Edwards alluded to it earlier.

22 Think about it for a minute. If a

1 busy practitioners takes the time out of his
2 practice to report an adverse experience, it's
3 important to them. And if a consumer calls
4 and reports it, it's important to her.

5 So I think the beauty of the
6 passive surveillance system is that it does,
7 in fact, identify those issues that we need to
8 evaluate that need a more formal epidemiologic
9 studies or pay particular attention to. So I
10 think the system is very important.

11 Secondly, though, I always get
12 confused when I take a look at the data in our
13 database, because it's not clear to me what a
14 spontaneous report is anymore. I look in our
15 database. We have a lot of legal reports.
16 We've got a lot of nonserious reports that
17 aren't that important. We've got a lot of
18 rumored reports that we can't even verify,
19 because we don't have the patient identifying
20 information or reporter identifying
21 information.

22 I think, if we want to use this

1 database to do any sensitive epidemiologic
2 studies, we need to make certain the data that
3 goes into the database is better. Therefore,
4 we need to accurately define what do we mean
5 by spontaneous report, what are the criteria
6 that we need for a spontaneous report, and
7 only enter those reports into the database.

8 Then the data might become more
9 meaningful and easier to interpret.

10 DR. STAFFA: June?

11 DR. RAINE: June Raine, EMEA. Our
12 real focus is understanding and maximizing the
13 value of spontaneous reporting, and if we
14 accept that the value of a spontaneous system
15 is the signals that it is capable of detecting
16 and then further downstream the regulatory
17 actions and communication and feedback to the
18 reporter and all these things, we have to
19 focus on how well do we understand that
20 output, the signal.

21 I don't know of any research that
22 has looked at different spontaneous systems

1 around the world to look at what a benchmark
2 might be on signals detected and when in the
3 product life cycle and so on.

4 I think, in operating those
5 systems, we have to be very clear about what
6 are our prime outcome is.

7 Secondly, Judy, I think you
8 mentioned that there may be other sources of
9 signals that we might be looking at in
10 longitudinal databases, population databases
11 and so on.

12 Therefore, I think once we have a
13 benchmark from spontaneous systems, we can
14 look at comparing the predictive value of
15 spontaneous and other types of data, such as
16 population databases, and in that area we
17 would have to look at how you actually can do
18 hypothesis generation and confirmation in the
19 same dataset.

20 So you see different types of
21 research emanating from the prime
22 consideration, which has to be what is good

1 enough signal detection, and what is
2 characteristics of the spontaneous database
3 that enables us to optimize that by quality,
4 by education, and so forth.

5 DR. STAFFA: Marietta?

6 DR. ANTHONY: I am Marietta
7 Anthony from the Critical Path Institute, and
8 I'd like to give very strong endorsement to
9 the passive surveillance system that FDA has,
10 and I think, if there has been any problem in
11 the past, it has been due to a lack of
12 funding.

13 We cannot just have this sort of
14 reporting without having the staff and the
15 tools to make sure that findings or signals
16 are generated and those are reported back.

17 So again, I guess one of my points
18 is that we've got to make sure that there is
19 adequate funding to support this.

20 Then, of course, to echo some of
21 the other points that are made, we've really
22 got to improve the quality of the reports to

1 the database.

2 Another point is, certainly, there
3 are other systems to collect these reports,
4 but we know that, in terms of detecting rare
5 adverse events, the FDA database is unique.

6 Then also there have been reports
7 of events that have been generated years after
8 a drug has been on the market that have only
9 been detected by this database. An example is
10 tamoxifen causing cataracts. This was a drug
11 that was on the market for 30-plus years, and
12 it was only detected in the 1990s.

13 So I think there's tremendous
14 value.

15 DR. STAFFA: Trinka?

16 DR. COSTER: Trinka Coster. I'd
17 like to first say that I think the spontaneous
18 reports are the tip of the spear, because
19 there is probably nothing as valuable as a
20 physician or a health care provider that
21 observes an event and writes a well written
22 report that would include dechallenge and

1 possibly rechallenge. I think that will
2 always be something that we will use to
3 further investigate.

4 As for improving reports, I'd like
5 to take a couple of ways of looking at that
6 as, one, with electronic medical records
7 coming to fruition in multiple hospital
8 settings, is the concept of extracting data
9 from those electronic medical records to
10 populate an adverse event report.

11 I would propose that there needs
12 to be an understanding of what is the
13 information that needs to be extracted to
14 improve the reporting, given that there will
15 be tools that you could automatically do that.

16 So is it important just to take
17 those events around the event that is being
18 reported? Do you need to go back 30 days, 60
19 days? Is there a problem list that needs to
20 be extracted with it? Does the allergy
21 section need to be extracted with it?

22 I think, to improve the automating

1 of a data that can go into a report once the
2 physician writes the narrative so that you get
3 an encapsulation of that patient would be
4 worth pursuing to understand what are the
5 other data elements that you need to enrich
6 those case reports.

7 Secondly is a concept of where do
8 physicians -- In order to comment on an
9 adverse event is where do we document adverse
10 events, because in reality, at the end of the
11 day, physicians need to communicate to each
12 other that something bad happened when a drug
13 was given.

14 Traditionally, the allergy section
15 has been limited, at least in some physicians'
16 concept, as to be only true allergies. I
17 think that concept needs to be expanded to
18 include other things besides true allergies,
19 but in effectiveness of the drug, drug
20 intolerance and how do we label those so that,
21 regardless of what electronic medical records
22 somebody is using, that physicians going to

1 different hospital sections know that I'm
2 going to put the information in there. Then,
3 similarly, if you extract that for your
4 MedWatch form, that you know what data fields
5 you are obtaining.

6 So it really is begging the
7 question, kind of like you've done with the
8 CDIS to standardize the way we've done
9 clinical trials, to really start looking at
10 standardizing the way some of this data is put
11 in so that people know where it is to extract
12 it, which then leads to education both for
13 health care providers of how do we use a
14 section, whether it be allergy and drug
15 intolerance or however you call it, is that
16 that's where I'm going to go to get my
17 information, because that's where I'm going to
18 communicate to the next doc about that the
19 drug doesn't work, because when you ask your
20 patient, the patient will say, well, it was a
21 little blue pill, and not really know why the
22 doc took them off of it.

1 So there really needs to be that
2 benefit to the physician. If I'm going to
3 document it, I know I'm communicating to the
4 next physician of something bad happened or
5 don't take this drug.

6 Also I would like to consider the
7 concept of improving reporting is -- I think
8 somebody mentioned it here, of what's the
9 benefit for the physician to report -- is to
10 look into improving that benefit to that
11 reporter. What's in it for me, so to speak?

12 When I report -- I have an event,
13 and I'm concerned about it, I can do a
14 literature review and at least get some
15 information, but that is time consuming.

16 If there were a website, so to
17 speak, that was one stop shopping to the FDA
18 that, you know, you have your daily meds, but
19 you also have, if it was a drug, information
20 about the structure of that drug so that I
21 understood that that structure also had a drug
22 in a completely different class, a therapeutic

1 class, but actually was very similar. And so
2 I might be more apt to report something if I
3 saw adverse events in another related drug
4 that I hadn't even thought was actually
5 related.

6 So I guess what I'm asking for is
7 possibly -- One would be to consider posting
8 a agreed upon safety profile with the number
9 of reports and signal detection, so that when
10 I report a adverse event, when I click onto
11 that website the next time, I see another
12 report that pops up and realize, hey, that's
13 my report, and actually it's going into a
14 signal and it has some sort of benefit for me.

15 Number two would be look at the
16 way you -- the labels. The labels are very
17 large, you know, very robust, but I don't have
18 the time when I have a 10-minute examination
19 for a patient to really look to that label
20 very quickly and get the information I want.

21 So one of the things to look at is
22 how do you improve an abbreviated label to

1 provide information to the practitioners, not
2 necessarily consumers but the practitioners,
3 that enables them to really get to the meat of
4 the factor of what happens when I give this
5 drug with this other drug? Does the
6 concentration go up or down? I mean, that can
7 be very visually demonstrated without a lot of
8 words.

9 So really new ways of data
10 visualization to communicate information to
11 the practitioners so that they can see that
12 something is in a post-marketing section.
13 What does that mean? It means that we don't
14 know much about it. And so that there is a
15 way of educating people at the same time when
16 they are looking for knowledge.

17 So I guess improving a knowledge
18 source for patient safety that very easily
19 enables people to see the literature, the
20 safety profile, what's known about it, the
21 drug abbreviated label, the more extensive
22 label. But basically, people need

1 information. Clinicians need information very
2 quickly, and will be more apt to report if
3 they see a clinical relevance and then,
4 secondly, if they see that that report meant
5 something.

6 It means two things, either to the
7 public safety as well as communicating to the
8 next physician who picks up that patient.

9 DR. STAFFA: Well, we had thought,
10 I guess somewhat naively, that we were going
11 to work through these questions one through
12 six. It's clear that we are not going to do
13 that.

14 So if I could just ask you to kind
15 of be looking at those questions now and
16 again. What we are thinking is -- What we've
17 tried to do internally is sit down and scratch
18 our heads and say what do we want to know?
19 What would we want to know? What would we ask
20 to evaluate this system?

21 So if you can look at that and
22 just see, have we thought about this the right

1 way? Are there things we are missing? Are
2 there nuances of questions you would like to
3 see us include? And again, I know you guys
4 are bringing up a lot of additional issues
5 which are very helpful, and we are capturing
6 them all, too. But if you could kind of keep
7 that in the back of your minds so that, when
8 we come away, we can actually -- because we
9 are going to have to go back to the shop and
10 look at the questions, and we would like to
11 make sure we got the input we needed.

12 Yes? Go ahead.

13 DR. MANASSE: I was intrigued by
14 question number 6, actually, that I would
15 probably personally rephrase: What do we know
16 about what we don't know?

17 I'd be interested in some
18 discussion about what have we picked up that
19 was totally unexpected that came from totally
20 outside of a spontaneous reporting system that
21 was just in itself something just so unusual
22 that we had never paid any attention to;

1 because my general sense is that we will
2 likely pick it up in the spontaneous reporting
3 system.

4 So whether or not this is a
5 relevant question, I guess, is what I'm posing
6 here.

7 DR. STAFFA: Any other thoughts on
8 relevance of question 6?

9 DR. JONES: Well, I think,
10 actually, this and question 4 -- it helps to
11 look at the health care system a bit and
12 understand the usual scenario of patients
13 running through a physician's office.

14 This relates to all components of
15 the system, because a physician is usually
16 very busy. One of the things I used to teach
17 medical students at Georgetown is just do one
18 simple thing: Put possible adverse effect as
19 part of your differential diagnosis.

20 I think what we just heard about
21 the electronic medical record is there is a
22 need at the point of care -- and there's a lot

1 of things in electronic medical records about
2 information at the point of care -- there
3 needs to be a reminder: Is there an
4 interaction? Is this an adverse effect?

5 Correlated to that is not looking
6 only at the physician but all the staff, the
7 nurse practitioners, the others in the health
8 care team, because we are moving more to
9 health care team.

10 To go back to the things we don't
11 know about, if you look at the usual profile
12 of practice, we don't usually do immunologic
13 tests. We don't usually do creatinines
14 routinely. We don't do a lot of tests that,
15 in fact, if they were done routinely, would
16 pick up all kinds of adverse events.

17 So if you look at the health care
18 system dynamic, you can identify -- you can
19 make a very large list of things that aren't
20 going to be detected maybe ever. Probably the
21 Fen-Phen issue was a fascinating identity of
22 something that wouldn't have been picked up

1 any way except someone was very thoughtful
2 about relating that to the drug.

3 DR. STAFFA: This whole side is
4 really quiet. Okay?

5 DR. EDWARDS: Judy, first of all,
6 Fen-Phen was picked up in the Netherlands
7 years before it was reported on the American
8 market, and I think that is one interesting
9 factor and relates to the global nature of
10 spontaneous reporting and the need to look at
11 a few reports from any country.

12 What I was actually going to talk
13 about, though, was in relation to question 6
14 and maybe questions 1 and 2 as well. I think
15 one issue is what happens to signals that we
16 find in spontaneous reporting and discard?

17 I mean, we are talking about the
18 things that we take on and we see move on.
19 What about the noise, so called noise, in the
20 system? Is it really noise or is there
21 something in there that would impact, perhaps
22 help us fine tune the system or to look at, as

1 we were saying earlier, drug misuse or abuse
2 even?

3 I think there are lots of issues
4 there that we need to look at.

5 DR. STAFF: This side wake up yet?
6 Dan?

7 DR. BUDNITZ: So a couple -- This
8 is Dan Budnitz from CDC. A couple of issues,
9 trying to relate to these questions.

10 First, let me start with an easy
11 comment. Number 4, what is the role of
12 reports by health care professionals and
13 consumers?

14 I think the consensus is health
15 care professionals certainly play a key role,
16 and I can say from CDC experience
17 investigating medical product related
18 outbreaks, infectious and otherwise, almost
19 all of them have been triggered by the astute
20 clinician, often picking up the phone and
21 calling someone at the other end.

22 CDC is fortunate in that we have

1 some intermediary. We have local and state
2 health departments where they initially do
3 some separating the wheat from the chaff,
4 let's say. So I think that is something that
5 a passive reporting system really needs to
6 preserve and something that, if you rely
7 solely on active surveillance, I think will be
8 lost. So that's one point.

9 In terms of looking at other
10 trends or problems that may be discarded in a
11 typical passive surveillance system like
12 misuse or abuse, I think passive surveillance
13 certainly can be helpful for signals, but to
14 identify scope and magnitude and burden, maybe
15 some other systems might be most appropriate,
16 population based systems which might involve
17 active surveillance.

18 DR. STAFFA: From our other
19 international colleagues, I'm going to pick on
20 our colleague from Health Canada to see if he
21 has anything he would like to put forward.

22 DR. BERG: Jason Berg from Health

1 Canada. Regarding the value, right now we are
2 -- In Canada we are having a dialogue with our
3 provincial governments on how we can
4 facilitate reporting, increased reporting. In
5 Canada, of course, provincial governments are
6 responsible for health care delivery.

7 What we've heard from them -- and
8 there's been a number of comments we've heard
9 across the table here, but one of the things
10 that's really struck us was this earlier
11 comment about communicating the value of the
12 reporting system, and it is strongly felt that
13 is a very key barrier.

14 In order to do so, because we are
15 very sensitive to, and the provinces are very
16 sensitive to the burden placed on health
17 professionals, the time burden for completing
18 the reports.

19 So we are looking at different
20 ways where we can target reporting
21 requirements, types of reports, and these
22 kinds of questions would really help us in

1 demonstrating the value of reporting in that
2 we are sensitive to maximizing the impact on
3 public health.

4 So different ways we can
5 selectively target sources of reports, but
6 also the types of reports.

7 DR. STAFFA: Thank you. Mike?

8 DR. COHEN: Back to -- Question 6
9 continues. Why don't we report? We had asked
10 people about this, because obviously, you
11 know, we work with the U.S. ISMP program for
12 medication reporting. We want to know what
13 stimulates the reporting.

14 Obviously, altruism is -- You
15 know, that's a big part of it, a person's
16 altruistic nature. But also -- and it goes
17 back to what Paul and I were saying a little
18 bit earlier. Knowledge that corrective action
19 will be taken is something that is really
20 important. So that kind of feedback.

21 Knowledge that others will benefit
22 from the report is important, and the

1 reporting is brief and uncomplicated. We'll
2 take a narrative and then follow up with
3 questions for important issues.

4 I think that would be very
5 helpful, but again it gets back to getting
6 back to people. They need to see that the
7 information they are providing is of value.

8 DR. STAFFA: Paul?

9 DR. STANG: So one of your
10 questions was what other questions would you
11 add to your list of six. A theme I'm hearing
12 is something along the lines of, as our
13 infrastructure changes with the electronic
14 health record, the personal health record, the
15 other thing that's occurred to me is sales
16 reps who are usually a point of contact for
17 some of these reports, the access that they
18 have and the initiative is going down.

19 More and more institutions are
20 saying no more sales reps. So potentially,
21 that source is going to be changing. So the
22 question I would have is: Is there an

1 opportunity with all these changes to impact
2 the system in a positive way?

3 I guess the first part of that I
4 think of are the electronic means that, I
5 think, have been mentioned over and over
6 again. But I'm not sure that is captured in
7 the spirit of any of the six questions that I
8 see, especially if this is going to be a
9 multi-year effort to think about.

10 You probably want to start
11 thinking about what are those things that you
12 could be doing now that would be helpful?

13 DR. STAFFA: Yes?

14 DR. SHARRAR: Bob Sharrar from
15 Merck. I would like to address question
16 number 6 also.

17 There will always be
18 underreporting. I'm kind of glad of that,
19 because I probably couldn't handle all of the
20 reports, if they were to come in. But I want
21 to tie this in with other activities going on
22 in pharmacovigilance, by which I mean

1 basically the risk management activities.

2 If you take a look at what they
3 want in a risk management plan, they want
4 pharmaceutical companies to be proactive in
5 terms of monitoring their products, and they
6 also want us to be focused on those important
7 identified risks, important potential risks,
8 and important missing populations.

9 I think we have to develop a post-
10 marketing surveillance system that helps us
11 identify what are the important issues that we
12 really need to pay attention to, because it is
13 not possible for us to pay attention to
14 everything.

15 DR. STAFFA: Yes?

16 DR. WATHION: I am Noel Wathion.
17 Coming back to question 6 and 4, it all
18 depends what you would like to achieve, of
19 course, and looking at the question,
20 underreporting is of particular concern, since
21 it may be to an underestimation of the
22 significance of a particular reaction.

1 Do you really want to know what do
2 we know about nonreported adverse events or
3 there have been studies in why we are not
4 reporting. Do you want to explore that much
5 more, the reasons for it, and what can be done
6 in order to stimulate that particular
7 reporting, rather than what do we know about
8 nonreported adverse events?

9 Perhaps a second issue, coming
10 back to what Ralph Edwards said and something
11 that we have also been confronted on in
12 Europe, you have this noise. You have a
13 signal which has been detected, but then a
14 decision is being made by regulators not to
15 pursue that particular signal, what has been
16 the rationale for it, because it is very
17 important later on in terms of -- I mean, the
18 general public is more and more interested in
19 transparency of operation.

20 So why are regulating authorities
21 on the basis of noise or the system that has
22 been detected, don't continue then in terms of

1 moving up the evidence. They are asking, for
2 instance, for an epidemiological study,
3 etcetera. That is also something we are
4 exploring.

5 DR. IYASU: Just, I think, to
6 clarify the question number 6, part of the
7 reason why we have that question is exactly
8 what you said, to link it to an action that we
9 can contemplate in the future with regard to
10 stimulating or reducing, actually,
11 underreporting.

12 There are studies that looked at
13 maybe characteristics of reporters. That may
14 predict sort of a reporting. Are there health
15 care institution specific factors that may be
16 related to reporting? There may be geographic
17 or regional or other parameters that might
18 actually have an impact on that.

19 If we could sort of identify those
20 issues, then I think we can sort of think
21 about best to stimulate reporting and reduce
22 underreporting. It also includes the quality

1 of the reports that we get.

2 DR. STAFFA: Now that we have kind
3 of tortured question 6 and 4, I'm wondering if
4 folks have comments on the others, again
5 bearing in mind, we are not asking you to
6 provide answers to the questions. That's
7 actually what we are going to be putting out
8 the contract to do the research to do.

9 So if you have thoughts, again
10 this is your chance to make sure we are asking
11 the right questions to get the answers to it.
12 At the end of the day, we don't want to say,
13 gee, what if they had only asked this.

14 DR. GOLDHAMMER: Alan Goldhammer,
15 PhRMA. I think, to address part of -- This
16 may be a little different way of looking at
17 some of these questions. I think we need to
18 document where the successes have come in
19 spontaneous reporting.

20 I mean, everybody points to the
21 very rare things like Stevens Johnson
22 Syndrome. Certainly, in the case of liver

1 problems, somebody goes to, you know, an acute
2 liver unit for transplantation. They find out
3 it may have been drug related. Those things
4 all get registered very early on.

5 We know what spontaneous reports
6 do very poorly, and that is where things have
7 a very high background and trying to -- you
8 know, the COX2 inhibitors were a classic
9 example there. If we were to rely on a
10 spontaneous reporting, I don't think that
11 would be -- That would never have been pulled
12 out of that.

13 So if we try to catalogue what are
14 the things that this does particularly well,
15 and then kind of building on the themes we
16 have heard to encourage health care providers
17 to focus in on that, and then as some of these
18 other things get built out as we move on, they
19 will address the high -- we hope they will
20 address the high background cases. But we
21 shouldn't fool ourselves in thinking that the
22 high background cases are ever going to be

1 resolved by improving spontaneous reports.

2 It's just going to make a lot more work for
3 everybody with, I think, very little payoff.

4 Then the other point on this is to
5 try to catalogue the kind of information that
6 we need in spontaneous reporting. I was
7 struck by the one slide that someone showed
8 about what the typical desktop looks like, and
9 I believe virtually everyone of those patients
10 was 50 years of age or older, probably such as
11 myself, on polypharmacy, which makes things
12 even more complicated. But I think you need
13 to have a better idea of what your
14 demographics are in terms of the reports that
15 are coming in, because that is going to be
16 very important to what the utility is.

17 So that might be another question
18 you want to ask as you go back and look at the
19 database.

20 DR. STAFFA: Okay.

21 DR. RAINE: June Raine. With
22 apologies to go back to number 4, I'm not sure

1 that we have truly captured the value of the
2 difference between health care professional
3 report and patient reports. Maybe I'm
4 speaking more from the European perspective,
5 and it is our focus as we are about to move
6 forward to fully embraced consumer reporting
7 throughout the EU, or at least that is what is
8 on the table at the moment, but really
9 thinking what Alan has just been saying.

10 Do we really know what value we
11 get? The patient is often the safety net, the
12 last person that really has all the
13 information at their disposal, given what Judy
14 has described as a sort of journey through
15 different health care providers.

16 If you take into account some of
17 our unknowns recently, such as the gadolinium
18 in the NSF or the intraocular fluffy iris,
19 you've got the person in the health care
20 journey who observed the ADR not being the one
21 who treated the patient.

22 So the patient role and what that

1 can offer us -- have we got good research to
2 fully capture that?

3 DR. MANASSE: I think a relevant
4 question is how can FDA more effectively and
5 perhaps more robustly develop relationship
6 with the practitioner community through the
7 societies and through the organizations that
8 work with them on a regular basis?

9 Most of the organizations spend a
10 lot of time, money and energy to develop
11 effective communications systems. They
12 prepare a whole variety of educational
13 mechanisms, from live conferences to post-
14 casts to all kinds of variations on a theme
15 of electronic communication.

16 They interact extensively with the
17 educational community. That is at least the
18 case in pharmacy. We work very, very closely
19 with the schools and the students and the
20 residents, and those individuals who
21 voluntarily participate in organizations are
22 the motivated proportions of the professions.

1 I think, to the extent that
2 professional organizations such as Joe's and
3 mine can look at not only incentivizing by
4 better communication with these individuals
5 about the data itself and how that data might
6 be used in clinical management of patients and
7 caring, but I think it could also get them
8 more engaged in the broader dialogue around
9 safety.

10 That is a high priority issue in
11 schools of pharmacy. I think, to that extent,
12 that is kind of the nature of the curriculum.
13 But on the other hand, the pharmacy
14 practitioners spend a lot of time,
15 particularly in hospitals and health systems,
16 working with their colleagues in medicine.

17 I think, to the extent that these
18 individuals can help facilitate that dialogue,
19 that again can be stimulated.

20 I think there is another area, and
21 that is to what extent can that practitioner
22 community help us engage in the development of

1 policy. They are the frontline people. They
2 see every day what is occurring, and can they
3 broaden a better understanding of the policy
4 development?

5 So to the extent that
6 organizations have their policy development
7 processes, which most of them do, what can be
8 done to help stimulate greater focus on these
9 kinds of issues?

10 DR. STAFFA: Judy?

11 DR. JONES: I would like to segue
12 from your comment and also Mike's comment
13 about the framework of reporting and
14 participation in the system.

15 Actually, the CDC has sort of a
16 model in the sense of the state health
17 departments and the infectious disease
18 reporting, and it seems like it's not a very
19 big leap to consider that.

20 The nice thing is that clinicians
21 get feedback from the statistics, at least in
22 Virginia. We know how many cases of

1 everything there are, and it is very -- It's
2 actually rather useful.

3 It occurs to me that the framework
4 of contributing to the public health by
5 reporting -- I don't think it's promulgated at
6 all in medical schools or pharmacy schools,
7 but in fact, this is a useful message for both
8 medical and pharmacy and other health care
9 practitioner schools.

10 Just a quick anecdote, because it
11 is so critical, and it is an illustration of
12 this. When I was at FDA, I got a call from a
13 physician in a pediatric intensive care unit
14 who said we are killing the babies. He
15 basically had five children who died because
16 of excess benzyl alcohol in the multi-dose
17 vials.

18 Long story short, this was
19 presented at a meeting. They found a number
20 of other cases, and probably estimated that
21 thousands of children were actually saved by
22 his reporting to that and FDA taking that

1 multi-dose vial off that.

2 He really deserved a Presidential
3 award. He saved lots of lives, and the
4 question always is, are there ways, are there
5 mechanisms, perhaps not so grandiose as that,
6 but ways of recognizing reporters who really
7 are contributing and have a tremendous amount
8 of leverage in the public health sense of
9 finding something that really is affecting a
10 lot of different individuals.

11 DR. GOGOLAK: One of the things
12 that I noticed in the discussion was the
13 relationship between policy and gathering the
14 data. One of the things, for instance, I
15 remember from the past is the Webber effect.

16 When you have spontaneous data as
17 opposed to a cohort study where you can
18 scientifically design it, you have a situation
19 where you don't know what the background is
20 like; and if you forgive a photographic
21 analogy, if you have to do color balance --
22 you know, you take a picture in fluorescent

1 lighting or out in daylight, you get the
2 picture, but it has a color cast, and that has
3 to be corrected.

4 I think of spontaneous reports as
5 having lots and lots of different color casts
6 and spontaneous biases and so on. So I think,
7 in this research that you are looking to do,
8 what would be very valuable is to understand
9 the relationship between the way you collect -
10 - for instance, there was a switch in policy
11 to not have nonserious reports after three
12 years.

13 It would be very interesting to
14 see if in the fourth and fifth year the kind
15 of data mining would change, because you are
16 changing the policy on the denominator.

17 I don't know how many other kinds
18 of things there are like that, but obviously,
19 we have to balance workload. I'm actually not
20 saying we should stop some of these policies,
21 because we might create too much work if we
22 collected everything. But if we understood it

1 and said, you know, after the third year you
2 have to adjust for this kind of -- you know,
3 like seasonal adjustments and so on.

4 So I think, you know, we might
5 have to get a little bit more subtle in some
6 of the questions when we look at what we are
7 trying to decide, because in a lot of cases,
8 if you have one really classic pivotal case,
9 you can decide, yes, there is a nice
10 relationship; but if you are doing it more in
11 a data mining situation where you are looking
12 at three or four cases and you are trying to
13 say, well, did the patient have a background
14 of the disease or a concomitant or something
15 else that could be causing it.

16 So that was the second major area
17 I would recommend. That is the relationship
18 between demographics -- you know, the patient
19 history -- and concomitant medications.

20 Sometimes we get very casual.
21 When I look at the AERS data, the suspect drug
22 is very well spelled and characterized and so

1 on, but the concomitant medications are
2 sometimes dot-dot-dot or spelled in kind of
3 strange ways, if the reporter isn't familiar,
4 especially if the drug is outside of his area
5 of specialty.

6 So these two areas might be very -
7 - I don't know where they fit in the six
8 questions. I also apologize -- I'm Victor
9 Gogolak from DrugLogic, and I'm on Panel 2.
10 So I don't know if my comments are allowed.
11 Thank you.

12 DR. STAFFA: Dr. Edwards?

13 DR. EDWARDS: I think one issue
14 that we need to add to this is the issue of
15 legislation and the effect of potential legal
16 action on decisions that are made on the basis
17 of this mass of information, which varies from
18 utter nonsense to real gold in terms of
19 decision making.

20 If we don't consider how decisions
21 are made on this basis, what decisions can be
22 made in a valid way, how much we can ignore in

1 this dataset, we are going to have a problem.

2 Well, we have a problem.

3 We have issues that come up where,
4 say, 100 reports are ignored because they are
5 all incomplete and, you know, one thinks,
6 well, are 100 people totally ignorant. And of
7 course, we have the other kind of situation as
8 well where utterly ridiculous reports form the
9 basis of considerable amount of work for
10 industry and regulators alike.

11 So I think the key question is
12 actually the sub-question of number 1: How
13 are these data best used in regulatory
14 decision making? And to actually investigate,
15 do post mortems of the impact of this data,
16 how the decisions were made is, I think, a key
17 point.

18 I just finally want to point out
19 that there's a conflict between a
20 communication tool, which I think we do need
21 to allow patients and health professionals to
22 tell us what they think are wrong with drugs,

1 and we have already discussed the value of
2 doing that.

3 It's bound to mean that you are
4 going to get more information, and a lot of it
5 isn't going to be terribly useful. What we
6 have to do is to be able to sort that out, and
7 we will be overloaded with stuff, and it won't
8 all be useful. What we need are the tools
9 that allow us to sort this out in a proper
10 way. Thank you.

11 DR. STAFFA: Back over here?
12 Marietta?

13 DR. ANTHONY: One of the areas
14 that I think needs research is in
15 communicating back with health care
16 practitioners, and the fact that I know that
17 you have several ways to communicate with
18 physicians, such as the "Dear Doctor" letter,
19 such as the MedWatch report.

20 Has there been any research to
21 ascertain the impact of these reports, you
22 know, how many physicians or how many

1 clinicians you reach? And more important, is
2 what the response is. What behavior does that
3 report then trigger?

4 Then are there any other research
5 projects in terms of communicating with
6 patients, because most of the focus has been
7 with practitioners? Does anyone think that
8 communicating with patients would increase the
9 value?

10 DR. STAFFA: I'm just looking at
11 my FDA colleagues now. Are other things like
12 that -- I believe there are.

13 DR. DAL PAN: there have been some
14 studies that people from FDA and others have
15 published about the impact of boxed warnings
16 or "Dear Health Care Professional" letters,
17 and it's been quite discouraging, actually,
18 that they haven't resulted in the kind of
19 changes in prescribing that they were intended
20 to produce. More systematic research, I'm not
21 aware of. It's really more anecdotal, case by
22 case.

1 DR. STAFFA: Would my colleague,
2 Judy Racoosin, have anything to add. She is
3 actually with FDA's Division of Drug Safety
4 Policy and Communication.

5 DR. RACOOSIN: There is I was just
6 going to add, there is a strategic
7 communication plan that has been recently put
8 together by CDER along with the Office of the
9 Commissioner.

10 So part of the question about
11 studying these various communications: There
12 have been several new types of communications
13 that have been released on a regular basis as
14 our office has grown to address new emerging
15 safety information, and there are public
16 health advisories and health care professional
17 sheets and briefings on safety evaluations
18 that are undergoing.

19 So while all these things are
20 being done, the strategic plan is coming up
21 with ways of studying what the impacts of
22 those are going to be. So there is probably

1 on some level some studies that are already
2 ongoing, but there is a much bigger effort to
3 really look at this in a comprehensive way.

4 DR. STAFFA: Thank you for chiming
5 in. Paul?

6 DR. STANG: I just want to draw
7 your attention to some of the work that I've
8 seen recently, one coming out of Bernard
9 Bergot's group about what are the
10 characteristics of a given report or series of
11 reports that actually triggers a bigger
12 decision.

13 The reason I highlight that is
14 because it may make sense to, for a second,
15 put aside serious and nonserious and focus on
16 what are the bits of information that really
17 do drive the decision at the end of the day,
18 and how best to collect that.

19 Kind of as a follow-on to that,
20 Anne Holbrooke and the folks up at McMaster
21 have looked at the same kind of question in
22 electronic health records and claims, and come

1 to some sense of what are the data fields that
2 feed in, and what are the critical ones, the
3 must haves, and what are the nice to haves at
4 the end of the day.

5 So again, it kind of crosses a few
6 of these questions, but the idea is what is
7 the minimum credible quality dataset that is
8 going to really drive a decision at the end of
9 the day.

10 DR. STAFFA: Thank you. Yes, Bob?

11 DR. SHARRAR: I would just like to
12 comment on what I call the challenge of post-
13 marketing surveillance. It's not an easy
14 game. By that, I mean if we give a patient a
15 drug and they get an adverse experience, that
16 adverse experience could be caused by the
17 drug, could be caused by the underlying
18 disease process we are trying to treat, could
19 be caused by a concurrent condition, could be
20 caused by a concurrent medication, or could be
21 just one of those rare unexplained background
22 events that occur in any population.

1 Our job is to collect the data and
2 analyze it to the best of our ability, and
3 when we look at a signal, we have to use then
4 clinical judgment. So some signals we are
5 going to overlook, and some signals we are not
6 going to overlook.

7 What I would like to see this
8 group do is see if they could develop some
9 kind of guidance documents that might help us.
10 For example, you know, when you take a look at
11 liver abnormalities, you think of Hy's Law.

12 Are there other -- Can we take a
13 look at when signals were identified, and then
14 take a look and see what got reported early in
15 post-marketing to see are there early signals
16 that we should be paying real close attention
17 to, because it may evolve into something more
18 serious?

19 Also, I think the other thing we
20 need from my perspective is we need better
21 background rates. You know, what are the
22 rates in the normal population? They are hard

1 to find and, when you find them, they don't
2 always pertain to the population you are
3 treating. But if we are going to compare
4 what's happening in the post-marketing
5 environment with background rates, then we
6 need some rates to make that comparison.

7 DR. STAFFA: Bob, I think you have
8 raised interesting questions about time, and
9 I think if you look at question 2, a lot of
10 what Mara has been doing is focusing, again,
11 on the life cycle of the product and looking
12 at time.

13 So if there are other thoughts or
14 issues that relate to how we approach this
15 concept of looking throughout the marketed
16 life cycle of the product, that would be
17 great.

18 DR. CRANSTON: I wasn't going to
19 address question 2. I was --

20 DR. STAFF: That's okay.

21 DR. CRANSTON: -- just going to
22 make some comments relative to some of the

1 other comments that have been made and some of
2 the other questions.

3 I think, first of all, I agree
4 very much with Henri that there needs to be
5 closer relationships between FDA and societies
6 that represent health professionals in terms
7 of trying to build better bridges both in
8 terms of getting information into the agency
9 as well as getting it out.

10 In that regard, AMA has been
11 working with FDA and some high prescribing
12 medical specialties on the risk communication
13 side, with Dr. Dal Pan. He is bringing up the
14 input side. Hasn't had a lot of success in
15 the discussions.

16 I have been at the AMA for about
17 26 years, and we were involved at the very
18 beginning with MedWatch, and we have tried to
19 help over the years. But you know, in my
20 opinion, physicians, frankly, are either
21 unaware of the program entirely, wouldn't have
22 a clue what to report, how to report, and have

1 also some concern about reliability of the
2 data.

3 So I think that -- and getting to
4 Dr. Stang -- his comments -- You know, if one
5 could clearly identify what is a high quality
6 report, if we are not talking about numbers
7 here, if we are really talking about quality,
8 and develop educational programs through
9 societies, you know, with constant
10 reinforcement -- Reinforcement is critical
11 here -- you know, maybe we can improve the
12 kinds of reports that will really be of value.

13 DR. STAFFA: Thank you. Dan?

14 DR. BUDNITZ: This is Dan Budnitz
15 from CDC. I was not going to address question
16 2 either, but maybe question 5 is a question.

17 DR. STAFFA: Someday someone will.

18 DR. BUDNITZ: Well, maybe question
19 5 is a question that I don't think has been
20 addressed too much.

21 Are there types of adverse event
22 reports that are not helpful for signal

1 detection? And maybe just take a stab at it
2 as a question to further look into, like in
3 your RFA, is maybe: Are reports of known
4 serious and nonserious adverse events more
5 efficiently examined using active surveillance
6 rather than passive reporting, where we might
7 have some population based datasets that can
8 really tell us more about the denominator of
9 exposure and the background rates of these
10 known events, and might that be more efficient
11 use of resources?

12 Also some of the ideas that were
13 raised about reporting, and maybe the public
14 health model -- I think there are a few
15 important things to note. One is that often
16 the public health reports are mandated --
17 mandatory to be reported, and they also are
18 often lab based. So there's lab based
19 reporting.

20 Finally, they typically have
21 pretty rigorous case definitions and pretty
22 rigorous requirements of what needs to be in

1 a report beyond a narrative, but other
2 characteristics of a proper report.

3 So those are some things that need
4 to be considered when making comparisons.

5 DR. STAFFA: Interesting point.
6 Yes?

7 DR. WATHION: I am Noel Wathion.
8 Coming to Question Number 2 --

9 DR. STAFFA: Thank you.

10 DR. WATHION: Well, I can give it
11 a try. I think it is a very difficult
12 question to answer and perhaps not only the
13 spontaneous reporting will be something that
14 has to be considered in this particular
15 respect. In fact, there are a number of
16 factors which will influence the time between
17 the approval and the first post-authorization
18 action that is being undertaken.

19 Perhaps some of the issues -- One
20 would be the safety database that you have in
21 place at the moment that you license a
22 particular project, and the extent of the

1 population exposure at the moment of approval,
2 but also how you are going to increase the
3 knowledge about the safety profile of the
4 medical product post-authorization and the
5 extent and the rapidity of population exposure
6 during the post-approval process.

7 You also have to take into account
8 the kind of products that you are currently
9 marketing and that you are going to license
10 some quite emerging therapies, etcetera, where
11 the benefit/risk balance perhaps at the moment
12 of licensing of a product could be a little
13 bit more tricky than it used to be. It will
14 depend on the risk management aspects and the
15 risk minimization measures that you are going
16 to introduce as well.

17 So the question is very
18 interesting. It is, I think, worth exploring,
19 but the answer may be a little bit more
20 difficult.

21 DR. STAFFA: You've raised a
22 couple of other factors. We had brought up

1 the issues that we have thought of that could
2 influence this timing would be -- Well, you
3 know, the type of regulatory action,
4 obviously, could differ and the nature of the
5 safety signal.

6 Obviously, you can look at the
7 source. You've brought up the extent of
8 population exposure. Are there other things
9 that we should be specifically looking at that
10 could strongly influence this relationship?

11 DR. JONES: Just a quick answer.
12 Judith Jones.

13 Looking at the prescribing of the
14 drug for what patients, when a drug gets on
15 the market, particularly if it has multiple
16 effects, it has creep, if you will, into not
17 only broader populations but ancillary uses
18 that are related to the indicated use, and it
19 changes the entire population, their whole
20 risk profile.

21 That is something that you as
22 regulators really need to have an

1 understanding of as you are looking at it.

2 DR. MANASSE: Henri Manasse. I
3 think one of the important questions to pursue
4 in this RFP might also be an examination and
5 characterization of all databases that may be
6 relevant to picking up information. Let me
7 give you an example of what I mean here.

8 We now have 35 million elderly
9 patients in our Medicare program who are
10 participating in the Part D benefit. The
11 insurance companies, most of whom administer
12 these pharmaceutical benefit plans, have in
13 addition to the utilization data -- that's the
14 claims data for the prescription drugs
15 themselves and their reimbursement -- they
16 also have access to the performance of Plan A
17 or Part A and Part B.

18 So are there ways, for example, to
19 link patient experience vis a vis doctor
20 visits and hospitalizations with use patterns
21 of medications? That's a very rich potential.

22 The Veterans Administration, I

1 think, is another example of a fairly robust
2 database that exists, and you all probably
3 work with the VA already. But my impression
4 is that many of the insurance companies are
5 getting into this kind of research as well,
6 and to what extent can that be helpful?

7 A number of particularly
8 integrated health systems who are either
9 completing or building better data systems may
10 also be resources.

11 So I think what I am trying to get
12 across here, I think there may be an
13 opportunity to get a better handle on broad
14 bases of access to spontaneous reports.

15 DR. STAFFA: Dr. Edwards?

16 DR. EDWARDS: Just a quick point
17 on the question 2, publicity both in the
18 general media and in the professional media.

19 DR. RAINE: June Raine. Can I add
20 one to our list, which is now that new
21 medicines have pharmacovigilance plans, are
22 they actually impacting on our goal to pick up

1 signals fast. It's what patients want. It's
2 what regulators want. Time really matters.

3 DR. STAFFA: Yes, Victor?

4 DR. GOGOLAK: Just a follow-up on
5 what Dr. Edwards mentioned. It's clear the
6 Internet and some of the solicitation of
7 adverse events has a clear direct effect.

8 We looked at a drug over-the-
9 counter that was taken off the market in the
10 year 2000. Half of the consumer reports were
11 after the year 2000. Many of those were years
12 later, and one or two or maybe even three were
13 two decades earlier.

14 That is a consumer reporting on a
15 subtle cardiac event 25 years for an over-the-
16 counter drug later. So, obviously, there's
17 got to be some way of filtering those things
18 out, in addition to the directed consumer
19 advertising, a physician being prone to
20 picking up something in the Journal of
21 Medicine, and then a bolus injection of
22 reports coming for a particular disease state.

1 There's also fashion in reporting
2 for things like torsade and rhabdomyolysis.
3 I think that would be very interesting to
4 investigate what the pattern is in certain
5 reactions being reported over time. Some of
6 them are related to a point that was made here
7 about doing certain testing. Only -- you
8 know, QT prolongation is going to be found in
9 a casual office exam.

10 So I think that might be a very
11 interesting area to examine. Thank you.

12 DR. SHARRAR: I would just like to
13 make one additional point. First of all, I do
14 think we need to stimulate reporting of what
15 physicians and health care providers think are
16 possibly adverse reactions associated with use
17 of a product. That means stimulated
18 reporting.

19 Now the question -- and we are not
20 going to tell a physician or health care
21 provider, no, we don't want that report. We
22 are going to take them all.

1 The question then becomes what do
2 we do with the report once we get it. The
3 point I want to make here is that that's a
4 regulatory call.

5 I work for a pharmaceutical
6 company. We do everything we can to follow
7 regulations. If you expect to make the
8 passive system work better, then the
9 regulatory agencies are going to have to come
10 together and decide what they want us to do,
11 and right now it's not clear to me.

12 DR. STAFFA: Other comments?
13 Trinka?

14 DR. COSTER: Just a last one, the
15 use of data mining and signal generation,
16 which we have been looking at both using the
17 public domain, AERS database as a way to
18 enrich the label and the safety concerns, both
19 for assisting physicians and reporting, as
20 well as in ourselves doing maybe DUEs or
21 MUEs, which are medication utilization
22 evaluations.

1 So that for, I guess, question 1
2 on the utility, if there are signals -- and as
3 you know, there can be a lag time between a
4 safety signal that is suspect, hasn't been
5 totally validated but is of concern because of
6 the events that it causes. Is there a way to
7 communicate that information in a way without
8 prejudicing that it is the drug, but it is
9 still of concern.

10 I mean, we certainly do that when
11 we list it in the post-marketing kind of
12 information, but when you do have a data
13 mining algorithm, that brings that up to a
14 unique event.

15 Is that something that can be
16 enhanced in this communication so that the
17 risk factors that possibly are associated with
18 that or the background rate that is of concern
19 is doing -- using that to spur MUEs,
20 medication utilization evaluations, using some
21 sort of risk reduction based on a possible
22 concern, for example, like methlyquin took

1 many years, and they were saying, well, you
2 know, the psychosis associated with methylquin
3 -- you also find people travel; they are
4 nervous; they have psychosis that is occurring
5 in the same general population rate that it
6 is. But if you use that information to say,
7 well, if people have these psychiatric risk
8 factors, maybe that will reduce the incidence.

9 Then you can at least do at the
10 hospital level, because we are all interested
11 in not having more of those cases in our own
12 patients, is using networks to do MUEs to see
13 if those risk reductions actually do have an
14 effect on -- So kind of combining the passive
15 surveillance with a directed surveillance
16 methodology to see what the impact of those
17 early signals do about actually making -- I
18 guess, to see what the impact is.

19 DR. STAFFA: Alan?

20 DR. GOLDHAMMER: I think I will
21 try to address question 2 here.

22 I think one of the things is to --

1 I know from the data that Mara has looked at,
2 it's a very heterogeneous group, because
3 certainly, if you look back at the 1991 in
4 that early cohort, probably there were very
5 few risk management plans that were put in
6 place.

7 You know, that has changed
8 considerably over the last four to five years,
9 as I think that we've all been more interested
10 in trying to look at safety issues early on in
11 marketing.

12 One thing that can be done, I
13 think, as part of a cohort study to look at --
14 it would probably have to be a very narrow
15 cohort study -- is to look at the first time
16 of action, regulatory action, and to link that
17 back to say, okay, what was the result.

18 What did this result from? Did it
19 come from the spontaneous reporting? Did it
20 come from the companies' own programs they put
21 into place where it might have been a post-
22 market study that identified something, or

1 something else?

2 So that we get a clear idea of
3 these actions, and what was the data that fed
4 into the action? Some of them may be multiple
5 things. It might have been suggestion from
6 the spontaneous report, follow-up by either
7 the FDA or the company in other databases, and
8 so forth. But again to see where is the value
9 proposition in what we are doing right now.

10 I think when we discussed this a
11 year and a half ago, it was to try to figure
12 out where do we get the biggest bang for the
13 buck in terms of resource investment, and that
14 was why the thought of looking later on in
15 product life cycle. Maybe we are putting
16 resources there that are not terribly
17 productive.

18 So we are going to need to
19 identify where the productivity is in terms of
20 using various different types of data.

21 DR. STAFFA: Judy?

22 DR. JONES: A footnote that

1 relates to questions 1, 3 and 4 has to do with
2 the whole quality issue.

3 I just wanted to point out that a
4 group in the International Society for
5 Pharmacoepidemiology and Drug Safety actually
6 developed a series of criteria for quality
7 reports for publication.

8 It also applies to reported
9 reports, but it's in Pharmacoepidemiology and
10 Drug Safety as well, and we are trying to get
11 it published elsewhere.

12 DR. STAFFA: We've got about five
13 more minutes. So if anybody has any kind of
14 culminating remarks on this issue. Victor?

15 DR. GOGOLAK: Gogolak at
16 DrugLogic. Just a quick question on the
17 narrative and lab results and so on.

18 You know, in the interest of
19 having a broader community look at these data,
20 is there any activity in the agency now to try
21 to make that public? At the basis, the
22 reporter and the patient are supposed to be

1 blinded, but of course, in the narrative there
2 is always the chance that there could be
3 indirect references and so on. But that's
4 always been a cry, at least for the last 10 or
5 12 years, that I've heard, to have redacted
6 narrative and lab information from these
7 reports.

8 DR. DAL PAN: It would be great if
9 we could have all the narratives out there
10 with the whole AERS database. The challenge
11 is, of course, redacting a few hundred
12 thousand reports a year. We don't have an
13 automated way to do that, and redaction has to
14 be done by people who are trained in
15 redaction, not people who are trained in
16 safety evaluation or something else.

17 So that is the biggest challenge
18 we have. There is no automated way to do it,
19 and it is very time consuming and resource
20 intensive is really the issue.

21 DR. STAFFA: Bob?

22 DR. SHARRAR: I just want to make

1 one final point. We are not the only people
2 who pay attention to the post-marketing
3 surveillance reports. I can assure you that
4 the legal profession is currently data mining
5 the dataset.

6 I know that there are people out
7 there that are opposed to immunizations that
8 mine the dataset for whatever information they
9 have in there, and they all believe that
10 everything we have in the database is, in
11 fact, causally related to the product, which
12 unfortunately is not true.

13 DR. STAFFA: Other final comments
14 from this group? Sara?

15 DR. RADCLIFFE: I think a theme
16 running through what I've heard this morning,
17 in a way, is that it is very difficult to
18 assess the value of adverse event reporting
19 without looking at what the alternatives are
20 out there.

21 That's a whole big discussion that
22 I'm certainly not recommending be included in

1 this study, because obviously, one could do
2 many studies on that topic. But I think it
3 might be valuable to add in a question or
4 perhaps focus down a question on, for those
5 areas where we know that adverse event
6 reporting does not work very well, what
7 alternatives are out there that might work
8 better, the reason being that I think we hold
9 onto to adverse event reporting in certain
10 situations because it's really the best -- or
11 we think it's the best that we have now.

12 There may be better ways to do it
13 now. There may be better ways that we can
14 develop in the future, so that over time the
15 value of adverse event reporting may change,
16 according to what the alternatives are.

17 So I think somehow getting at that
18 question would be very helpful.

19 DR. STAFFA: Okay. Solomon?

20 DR. IYASU: Well, I think the
21 discussion has sort of considered all the
22 questions that we have, but there is one

1 thought that is going through my mind right
2 now in terms of assessing the value of adverse
3 event reports, spontaneous reports and the
4 issue of framing it.

5 From whose perspective do we
6 actually measure that value? I'm wondering if
7 there are some comments that people have on
8 that.

9 DR. EDWARDS: I have a very quick
10 response to that. Everything should be done
11 from the patient's point of view. If we don't
12 see that the end result is improving patient
13 care -- and that is slightly different from
14 public health.

15 I think we have to do public
16 health as well as individual patient care, and
17 the information must go back to enable the
18 best patient care that we can provide.

19 DR. JONES: Another perspective
20 really has to do with the Joint Commission's
21 requirement, that adverse reaction reporting
22 systems be set up in hospitals, and many -- I

1 think many of these really have their primary
2 function in looking at quality of health care
3 in the institution, such as informed reactions
4 and simple things that are not of interest to
5 the FDA but are certainly of interest in the
6 quality of health care.

7 DR. STANG: I had approached you
8 at the break about this word value, because I
9 think it carries with it -- and I know it's a
10 tricky concept. It may make more sense to
11 think of it in more descriptive terms and
12 describe, in a sense, what the impact is to
13 the various stakeholders around the table.

14 I think when you say value, people
15 think of cost/benefit and infrastructure and
16 tradeoff, and I don't know that that is
17 necessarily the concept that you wanted to get
18 across.

19 DR. STAFFA: Good point. Bob, I
20 think you are going to have to be our final
21 comment.

22 DR. SHARRAR: All I could say is

1 accurately describing the safety profile of a
2 product benefits everyone.

3 DR. STAFFA: Okay. Now it is time
4 to move into the open public part of our
5 discussion, and I'm wondering -- We have Dr.
6 Patel had registered as wanting to make some
7 comments. I'm wondering if Dr. Patel is here
8 and if he could come up and use one of the
9 microphones, that would be great.

10 Dr. Patel? No? Okay. Well,
11 since Dr. Patel has not arrived, I think what
12 we would like to do is use some of this time.

13 I know Dr. Gogolak has joined
14 Panel 1, even though he is on Panel 2, and I'm
15 wondering if there are other folks from Panel
16 2 who are seated out in the audience who might
17 have some comments and thoughts that they
18 would like to share.

19 You can imagine, it was rather
20 difficult to differentiate folks' expertise as
21 to which panel they fit into so clearly.
22 There are folks who could serve equally well

1 on both.

2 So if there are folks from Panel 2
3 who have comments and would like to step up to
4 the mic and add to the discussion? Okay,
5 Panel 2 is shy.

6 Go ahead, Fran. Please, for
7 transcription, if you could just identify
8 yourself before you make your comments, that
9 would be great.

10 DR. CUNNINGHAM: Fran Cunningham,
11 Department of Veterans Affairs.

12 I think I have a couple of
13 questions. I don't know necessarily -- or
14 comments. I don't know necessarily where they
15 fit in question number 1 or question number 2.

16 A lot of them have been discussed,
17 but I'm going to bring them back up again and
18 probably try to frame it in a context inside
19 of a health care system and where you may
20 relate a regulatory system.

21 The first one is: What is the
22 value to the patient safety collecting AEs

1 through a passive surveillance system, which
2 is question number 1.

3 That is, when I looked at the
4 diagram that was put up by Mara earlier -- and
5 I can't quite remember -- I think it was Slide
6 Number 11 -- and looking at the product that
7 had been on the market or the products that
8 had been on the market for 16 years, it's very
9 evident that there are still problems that we
10 are picking up, and why is that the case?

11 I think it was mentioned. I think
12 the case may be twofold. One may be the
13 patterns of utilization where I think you very
14 well sit in a place that can inform us, the
15 public, on the patterns of utilization, the
16 drug being used in different populations.

17 So I take a drug like the
18 anticonvulsants that started out in one given
19 area, move to another area but now the
20 majority of these agents are used as mood
21 stabilizers in a patient population where you
22 have quite a bit of drug-drug interactions.

1 So the signal that you may be
2 detecting may be different when it was
3 marketed versus what we are seeing, and you
4 are in a perfect position to inform us of what
5 to look at, and that's based on the patterns
6 of utilization. That's my first comment.

7 My second comment deals with
8 utilization of how there are health care
9 systems or hospitals that use spontaneous
10 reporting systems, because we have to, and the
11 way we use it was brought up earlier. We use
12 it for systems changes or system level
13 interpretations.

14 Quite often, the adverse events
15 that we see are the common ones, the ones you
16 would expect to see, and also from the drugs
17 that are used most commonly in the system.
18 But when we go back to look at why we are
19 seeing the adverse events, it's how they are
20 being used, and quite often that may be what's
21 happening in your system. The drug is being
22 used in a much higher dose than what it should

1 be used.

2 The drug is now being used in a
3 patient population in which the end organ
4 function has altered, and so although the dose
5 that is being recommended is now being used in
6 the elderly population, you have more adverse
7 events that are popping back up into your data
8 system.

9 So I think there's things that you
10 can look at and give back to us, but health
11 care systems can also give it back to you.

12 That's it.

13 DR. STAFFA: Thank you, Fran.
14 Anyone else from Panel 2?

15 DR. LACEY: Yes. Thank you. If I
16 could introduce myself, I'm Gary Lacey from
17 the Therapeutic Goods Administration in
18 Australia. That's the national drug regulator
19 in Australia. I head up the Adverse Drug
20 Reactions Unit there.

21 In terms of the value of
22 spontaneous adverse event reporting, I would

1 just like to make one point, because it was an
2 issue that occurred in Australia several years
3 ago, and it enabled a quality control problem
4 to be identified, something that wouldn't be
5 identified through a proactive monitoring
6 program, in that we identified a small blip in
7 adverse psychotic events to a travel sickness
8 medication.

9 What that enabled us to do was to
10 actually investigate the problem and find out
11 that a contract manufacturer who had been
12 making that particular product actually had
13 some allegedly systematic flaws in their
14 manufacturing process which led to a consumer
15 recall of many hundreds of different
16 medicines, mainly complementary medicines, I
17 have to add.

18 I think it's worth noting the
19 value in that sort of scenario.

20 DR. STAFFA: Thank you. Good
21 point. Dr. Wolfe?

22 DR. WOLFE: Just on two of the

1 questions. One, on the value I --

2 DR. STAFFA: I just need you to
3 state your name.

4 DR. WOLFE: Sid Wolfe, public
5 citizen. There are a few published papers
6 from Spain, France, here, other countries that
7 point out that the overwhelming majority of
8 drug withdrawals, for example, are
9 precipitated either exclusively or certainly
10 heavily by spontaneous reports, and that is
11 not surprising, because we are talking about
12 events that are relatively rare, that don't
13 have a high background incidence.

14 It's been mentioned before, but
15 hepatic toxicity has been the classic example
16 of that.

17 So I think that the value is quite
18 clear, and it isn't as though it wouldn't be
19 also helpful to do some more active
20 surveillance, whether it's FDA using some of
21 these large HMO databases or anything else.
22 It's not either/or. It's both.

1 The only other thing I wanted to
2 comment on was the question about what can we
3 do to stimulate more and/or better, higher
4 quality reporting.

5 The first is just an anecdote.
6 When I was a medical resident 45 years ago or
7 43 years ago, whatever it was, the CDC was
8 then paying -- or the FDA, sorry, was paying
9 medical officer, house staff, \$25 which went
10 into their refreshment fund, a preferable
11 alternative to free lunches from drug
12 companies, and really high quality reports
13 were coming out of that.

14 The FDA conducted a very
15 successful experiment in Rhode Island about
16 20-plus years ago. It was published in the
17 JAMA in 1980, I believe, and they showed that
18 with proper cheerleading, stimulation, there
19 was a seventeenfold increase in adverse
20 reaction reports, and as soon as the
21 cheerleading stopped, it went back down again.

22 The third example is FDA's own Tom

1 McGinnis, who is a hospital pharmacist. I
2 think the role of hospital pharmacists is key
3 here.

4 I am a physician, not a hospital
5 pharmacist, but the quarterbacking role of a
6 hospital pharmacist going on rounds and
7 helping medical students and residents and
8 attendings and everyone else to recognize the
9 importance of adverse drug reactions can't be
10 underestimated.

11 Tom, I don't know if he's still
12 doing it, but he was regularly going down to
13 George Washington once a week, making these
14 rounds, and reported that there was an
15 enormous increase in adverse reaction reports,
16 just by educating people.

17 Along the educating people line, I
18 think that we need to encourage professional
19 societies to do things such as including board
20 questions, and it shouldn't take the
21 importance of a board question to get someone
22 aware of it, but that will work.

1 If someone believes that part of
2 the ethical responsibility of a physician is
3 reporting adverse drug reactions and it's on
4 board questions, and it's part of continuing
5 medical education, aside from the obvious
6 inclusion, which is not there -- I think Judy
7 Jones is right. I don't think it's taught in
8 medical schools anymore.

9 There are just all sorts of
10 avenues of getting more of the more serious
11 events, which at least, if they don't start in
12 the hospital, wind up in the hospital. You
13 know, our figures are there are A million and
14 a half people hospitalized every year with
15 adverse drug reactions. Those are estimated
16 based on extrapolations from smaller studies,
17 but they are going on in all hospitals, and I
18 just don't think they are being captured.

19 So I just strongly support more
20 roles of hospital pharmacists making rounds.
21 UCSF started this a long time ago in
22 collaboration between the Department of

1 Medicine and the Pharmacy School.

2 So I'm very optimistic about any
3 of these being tried, retried, expanded, to
4 get more accurate and meaningful hospital
5 based adverse reaction reporting.

6 The rest is for this afternoon.

7 DR. STAFFA: Thank you. Anyone
8 else from Panel 2? Dr. Kramer?

9 DR. KRAMER: Judith Kramer from
10 Duke University.

11 Dr. Edwards very eloquently
12 pointed out the value of spontaneous reports
13 from the actual patient, but I think one of
14 the things that was touched on by one person
15 here, but I think we need to emphasize a
16 little bit more, is we need to look at the
17 changing external environment in terms of
18 where these things are coming from.

19 Already, we have a situation where
20 the vast majority of reports are not coming
21 directly from patients. They may be
22 indirectly coming from patients, but on top of

1 that we have the influence of the Internet and
2 the blogs and stimulated discussion groups.

3 I've really been struck by the
4 groups that are really concerned about vaccine
5 reactions, etcetera. I think we need to keep
6 that in mind when we think about the future
7 face of "spontaneous" reporting becoming
8 influenced reporting and biased reporting.

9 So I don't know what the answer
10 is, but I just wanted to underline that.

11 The next comment -- Maybe it's
12 appropriate for this afternoon, but I at least
13 want to raise it.

14 The thing that's been bothering me
15 as I have listened to this morning's
16 conversation is one of, if you are going to do
17 research, let's talk about what the
18 fundamental question is, and let's talk about
19 definitions.

20 One of the things that bothers me
21 is how we brush over the definition of "a
22 signal." I mean, I understand that Mara

1 started with a regulatory action.

2 All right, but what happens before
3 that regulatory action? And if we are going
4 to do research on whether spontaneous reports
5 influence signals, everyone has a different
6 definition of a signal, and I think we are
7 going to be all over the place in terms of the
8 results we get.

9 So I just want to highlight that,
10 and that's probably a comment for this
11 afternoon.

12 DR. STAFFA: I think that is very
13 helpful. Thank you. DR. DAI: My name is
14 Waju Dai from Sanofi-Aventis, and I have two
15 questions for the panelists.

16 The first one is regarding the
17 question for consumer reports. I hear people
18 talking about we need a place for patients to
19 voice their concerns, and I heard about OTC
20 products. There are no physicians as
21 intermediary now. But regarding the
22 prescription medications, especially within

1 early years of marketing, I'm wondering
2 whether panelists can comment on the value of
3 consumer reports.

4 Frequently, the consumers don't
5 know the exact diagnosis. So you do need the
6 health professional's confirmation and help
7 you really elaborate on these events; and if
8 you have more consumer reports with, probably
9 will just really make your database much
10 bigger but difficult to assign the signals.

11 Definitely, I think there are some
12 roles for consumer reports, but I was
13 wondering whether the panelists could comment.
14 To me, sometimes like the counterfeit
15 products, the quality issue of the product per
16 se -- maybe sometimes the physician may not
17 know. Maybe you need to have physicians.

18 So it's not really specific for
19 some AE per se, but for other aspects. So
20 that's my first question for the panelists.

21 You want to continue with a second
22 question or you want --

1 DR. STAFFA: Well, I appreciate
2 you raising the question. I'm not sure we're
3 trying to answer the questions today, but
4 that's a great question that we hope to answer
5 in this research. But go ahead with your
6 second question.

7 DR. DAI: Okay. My second
8 question is actually toward Dr. Coster for the
9 PhRMA defense database.

10 You know this database is
11 automated medical records, like insurance
12 claim database, because usually when we talk
13 about adverse events that were not detected in
14 clinical trials, if you want to use automated
15 medical records -- I'm sorry, I said again --
16 claims record linked database, usually that
17 only has the prescription, the diagnosis made,
18 but not really the progress or even side
19 effect.

20 There are codes for that, but I
21 don't think physicians use that. In fact, I
22 believe when physicians report adverse events,

1 they are not really just for -- most of the
2 time, they are not really just for reporting
3 purposes, but rather to talk to manufacturers
4 to get more information about whether there
5 were other event experience by the company and
6 how to manage the patients with such events.

7 So in that regard, I'm wondering
8 with the PhRMA defense, because I talked with
9 somebody who knows the data saying that you
10 have much better quality data, because you can
11 tell the physicians in the PhRMA defense to
12 code pretty much everything you want him to
13 code, which you couldn't do with the regular
14 practicing physician.

15 So I'm wondering how good is the
16 data from the PhRMA defense for side effects.

17 DR. COSTER: I don't think we can
18 tell people to code better. I wish that were
19 true. And our data is improving with ALTA,
20 which is our electronic medical record, and
21 they are using some tools to try to
22 automatically code.

1 They are improving the way that
2 physicians can code and having associated with
3 the clinics folks who assist with coding and
4 relooking at the medical records. But I do
5 not think that we can tell folks to code
6 better or to code.

7 So I think that's still a
8 challenge in the military records system, but
9 I think it is vastly improving each year that
10 we use the electronic medical record system.
11 And as for over-the-counter medications, JCHAO
12 does require physicians to -- or at least the
13 health care providers to ask and query about
14 what over-the-counter medications they are on
15 as well to include supplements.

16 The problem with that is, without
17 a pick-list for supplements, you could only
18 imagine the kind of information you get put in
19 for what the actual person says they are on
20 and how that is placed into a database.

21 Then the question is where do we
22 put those OTCs and supplements in the -- do

1 you put in the nondispense part of the
2 pharmacy record?

3 So I think there's some challenges
4 with that of structured areas to put that
5 information in so that you could data mine it
6 or extract it in a known place. But JCHAO
7 does require at every visit the patients to be
8 queried, and the military does do that.

9 At every visit the patient is
10 asked about what over-the-counter medications
11 they are on, and that is documented somewhere
12 in a medical record.

13 DR. STAFFA: Thank you. Are there
14 any other panelists from Panel 2 that would
15 like to comment? Fran, a second round? Sure,
16 we'll allow that.

17 DR. CUNNINGHAM: Just one round,
18 because Judy told me I needed to comment.
19 This will kind of, I guess, answer both of the
20 questions in something you raised earlier,
21 Trinka.

22 That is, one of the programs that

1 we have inside of the Department of Veterans
2 Affairs, and that is in our electronic medical
3 record; and as a physician or a practitioner
4 is inputting a drug or ordering a drug, then
5 if a patient has either experienced a drug
6 interaction or has a known allergy, that is
7 listed so that the next time a practitioner
8 tries to order that, that pops up and prevents
9 them from, hopefully, ordering that again.

10 So that's definitely something
11 that we have, which is a feedback mechanism.
12 One of the things that we didn't have until
13 recently was the ability to extract all that
14 information, roll it up into a national
15 system, which is now available.

16 One of the things that we have
17 found from our pilot project is that
18 physicians do a very good job or practitioners
19 do a very good job at the point of care
20 finding out if a patient has had a reaction,
21 and the patient also does a very good job of
22 corresponding with the practitioner.

1 So if there is a way to begin to
2 look at both of those datasets, then you can
3 probably enhance some of the spontaneous
4 reporting efforts.

5 That is one of the things we are
6 doing with a pilot project now, and we are
7 seeing that that electronic medical record, by
8 far, is better at capturing the reported
9 adverse events. So that is something that may
10 be thought about in the future, but it's also
11 something that helps our practitioners now in
12 not re-prescribing, hopefully, drugs that have
13 adverse events.

14 DR. COSTER: I would like to
15 comment. Actually, the military does -- Prior
16 to -- We have the pharmacist printout for our
17 practitioners of the medication list that they
18 are and prior to seeing the health care
19 provider, each medication is gone over by the
20 nurse prior to being seen to ask if there is
21 any problem with that medication.

22 My only concern is I don't think

1 we've ever tested to ask how often is that
2 placed into the allergy section to understand
3 is the thing documented in the allergy
4 section, is the thing documented in a problem
5 list or is the thing documented somewhere just
6 in the medical record.

7 So if it was thought that we
8 weren't documenting allergies, I want that
9 clarified, that we are documenting it. I'm
10 just not so sure that we are systematic in
11 ensuring that it is documented in a single
12 place that is reproducible and known.

13 In addition, we do use our first
14 data bank and other methodologies. So when
15 physicians do write a -- go to prescribe a
16 medication, it queries the allergy section as
17 well as other medications they are on.

18 So drug-drug interactions are
19 warned to providers. Prior to being able to
20 fulfill that script, they have to override
21 that warning if they feel that the warning
22 didn't really matter to that patient.

1 I think we are looking at new
2 pharmacy data transaction systems to put in
3 there. So right now, when I make an order
4 entry for a patient, I am queried why I am
5 stopping that medication, but that information
6 only goes to the pharmacy department.

7 One of the things we are trying to
8 look at is actually exporting that information
9 to the health care provider as a way of
10 communicating, because it is not really just
11 a pharmacist that needs to know that, but it's
12 really the physician as well, because that
13 information is needed by others.

14 So although we have some of the
15 steps, we do use, as I said, First Data Bank
16 that queries the known drug interactions
17 associated with what the pharmacy medications
18 are that the patient is on.

19 For the military, we have a very
20 complete database of pharmacy, which includes
21 all mail order, all retail as well as
22 everything that's gotten in our treatment

1 facilities. So it's a very comprehensive
2 record of their drugs that they are on, and it
3 will query.

4 Anytime I go to write a new
5 script, it will query that database of the
6 pharmacy against known drug interactions and
7 flag the physician right there.

8 DR. STAFFA: Okay. Thank you,
9 Trinka. If there are other folks in the crowd
10 that would like to make comments or suggest
11 questions, if you could just go up to one of
12 the microphones and flip it on, and just
13 please preface your comments by stating your
14 name and your affiliation for the record.

15 DR. PAULS: The switch for the
16 microphone is on the bottom, and they are just
17 turned off to save the batteries.

18 DR. RODRIGUEZ: I am Evelyn
19 Rodriguez, and I'm from Bayer HealthCare
20 Pharmaceuticals, and my comments are my
21 personal opinion and not those of the company.

22 I just wanted to make a

1 suggestion, that perhaps the FDA can list
2 medical events of special interest and/or
3 populations of special interest such as
4 children, and communicate this to patients,
5 but more importantly, to the provider
6 community.

7 Also, I think that, much like the
8 U.K. system in terms of alerting physicians
9 and pharmacists on new medications that are on
10 the market, perhaps one can even narrow that
11 down to NMEs that have been newly approved,
12 rather than drowning requests with all newly
13 approved drugs. Thank you.

14 DR. STAFFA: Thanks. Yes?

15 DR. LAUDON: Good afternoon. My
16 name is Mark Laudon. I am with Aeries Global,
17 and we deal with a lot of customers throughout
18 selling of software to deal with the
19 processing of spontaneous, amongst other types
20 of safety cases, and we see a lot of barriers
21 that companies throw up for themselves,
22 unintentionally or as a result of

1 misunderstanding of regulations or differing
2 of regulations between different environments.

3 So a question I would like to
4 propose, and this is a personal suggestion,
5 because we thrive on the complexity -- but a
6 question I would like to propose is that one
7 of the questions be: Are there any barriers
8 or perceived barriers by which, once a
9 spontaneous report has been reported to a
10 company, that will prevent its accurate and
11 timely transmission onward to all interested
12 parties, so that, for instance, a case can be
13 reported identically and preferably with all
14 the pertinent data to all of the interested
15 agencies?

16 That would include such
17 complexities as in Europe we have reporting
18 currently to multiple agencies, and we have
19 the issue of data privacy as one where the
20 privacy rules differ enough that people can --
21 companies can create for themselves the belief
22 that they are not allowed to transmit certain

1 data.

2 Some companies throw up those
3 barriers. Others ignore them at their peril,
4 and it would be nice if we could ultimately
5 deal with harmonization issues in this and
6 say, okay, what barriers are there, and
7 therefore, how do we address those barriers in
8 such a way that all of the areas that are
9 represented here are participating on an equal
10 playing field. Thank you.

11 DR. STAFFA: Thank you. We have a
12 few more minutes, if there are other comments.
13 yes?

14 DR. KELLY: My name is William
15 Kelly. I work for myself in drug safety
16 consulting.

17 I ask myself when I come to one of
18 these things, what is the goal of post-
19 marketing surveillance? And as I listen to
20 discussion, I get the impression that a lot of
21 people feel that it is to identify signals
22 that can be further investigated. However,

1 from my perspective, it is to identify as
2 quickly as possible problems with drugs after
3 they are marketed to prevent patients from
4 being harmed.

5 You talk about nuance. I think
6 there is a nuance there. I would suggest that
7 the latter definition for the goal of post-
8 marketing surveillance would be the one that
9 would be optimal.

10 In Georgia, when I lived in
11 Georgia, we used to have an expression about
12 dogs. You can turn a hunting dog into a
13 lapdog, but you can't turn a lapdog into a
14 hunting dog.

15 The way post-marketing
16 surveillance is structured today, we got a
17 lapdog. And that dog don't hunt. And the
18 reason why he doesn't hunt is it takes too
19 doggone long to identify a problem with a drug
20 after it is newly marketed.

21 Is anybody around the table happy
22 with 2.6 years that goes by? In the

1 meanwhile, thousands of patients are hurt by
2 medication. Some of them die.

3 I was disappointed in the response
4 to Dr. Manasse's initial question that he
5 asked: Should we try to improve spontaneous
6 reporting or should we look for a better
7 system that more quickly identifies problems
8 with medication?

9 Danny DeVito in "The Color of
10 Money" talks about a buggy whip. He says, I
11 bet you the best buggy whip is made by the
12 very last person that made buggy whips. Are
13 we making spontaneous reporting the best that
14 we possibly can, in the meantime avoiding or
15 not really thinking about what the potential
16 would be in the society today where everything
17 is electronic.

18 I think after surveillance and
19 electronic surveillance is the key to
20 everything. And I look at the money being
21 spent on spontaneous reporting. The
22 pharmaceutical companies, the amount of money

1 they are spending on spontaneous reporting,
2 the amount of money that the FDA -- I used to
3 work at the CDC. I know how much theirs cost
4 and how much it costs to keep that system
5 going.

6 Refocoxib was a chipping point in
7 the eyes of the public and the media. They
8 want to know why does it take so long to
9 identify serious problems with medication
10 after they are newly marketed drugs, and I
11 think we are foolish to ignore that.

12 My own mother was harmed by that
13 medication. That took a long time for us to
14 discover, and I just appeal to this body. I
15 know that in September or October you got more
16 money. The Food, Drug and Cosmetic Act was
17 recently revised. You got approval to require
18 post-marketing surveillance. You got more
19 money to do it.

20 My question is what are you going
21 to do with that money? Are you going to put
22 that money into more active surveillance or

1 are you going to put that money into
2 spontaneous reporting?

3 DR. STAFFA: Thank you for your
4 comments. We have time for about one more.
5 Judy Racoosin.

6 DR. RACOOSIN: I want to agree
7 with what's already been said around the
8 table, that I think one of the most crucial
9 points is to train health care providers in
10 training how to fill out a good quality
11 report.

12 The reason I came up, the question
13 that I want to add is that what we have
14 observed over many years is that the best
15 information you get is on the first discussion
16 with the health care provider who is
17 reporting.

18 What happens over time is, as more
19 questions come up that you want to know about
20 the case, the likelihood of the reporter to
21 respond to that query goes down rapidly.

22 The thing that we never -- or that

1 I haven't really observed is, you know, when
2 that phone call comes into the pharmaceutical
3 company, to some degree -- you know, and I
4 think it is variable across companies, but to
5 have a very detailed template of the kinds of
6 questions to follow up with when the reporter
7 makes the report, so that I'm not -- I mean,
8 this has happened more times than I can count,
9 of getting a report of hepatotoxicity with
10 transaminases and no bilirubin, and then you
11 try to go back and get the bilirubin and, you
12 know, they've moved on to the next thing.

13 So I guess that's the question
14 that I'd like to pose, is having standard,
15 ready responses to the kinds of reporting that
16 comes in so that all of the important
17 information is collected on that first
18 interchange, and so we have the information we
19 need and we don't have to try and get more
20 contacts with the reporter, because of the
21 likelihood of getting those is exceedingly
22 small.

1 DR. STAFFA: Thank you. And I
2 would like to thank everyone for all of your
3 thoughtful input this morning. We really
4 appreciate it.

5 I am going to turn over to Lana,
6 who is going to talk to us about some
7 logistics.

8 DR. PAULS: I would like to echo
9 Judy's sentiment here. Thank you so much for
10 joining us on Panel 1 today.

11 I will ask, for those of you on
12 Panel 1 that can remain for the afternoon, we
13 would definitely appreciate your comments. At
14 the same point in time, if you could please
15 take your things and sit on the side so I can
16 prepare for Panel 2, that would be much
17 appreciated.

18 Just to let you know, there is a
19 wonderful cafeteria upstairs. They are
20 prepared for 100-some people. So they are
21 ready to get your food orders up there, and we
22 will convene strictly at 1:15 today.

1 Thank you so much.

2 (Whereupon, the foregoing matter

3 went off the record at 12:15 p.m.)

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A F T E R N O O N S E S S I O N

Time: 1:15 p.m.

DR. IYASU: Welcome to the
afternoon session of this public workshop. I
am Solomon Iyasu. I'm the Division Director
for Epidemiology at the Center for Drug
Evaluation at FDA.

This afternoon we are going to
talk about research approach and methods.
There were a number of panelists this morning
who discussed the questions, the key questions
that would have to be addressed in this
initiative.

Since there are several new
members who have joined us and, actually, the
panel in the afternoon is completely different
except for a few people who are overlapping,
I would like everybody to get up and introduce
yourselves. State your name, your
affiliation, and speak directly into the mic,
because people in the back can't hear very
well.

1 DR. STAFFA: Judy Staffa, Acting
2 Associate Director for Regulatory Research in
3 the Office of Surveillance and Epidemiology,
4 Center for Drugs at FDA.

5 DR. PAULS: And I am Lana Pauls,
6 the Director of the Quality Management staff,
7 albeit I am on detail to the Office of
8 Surveillance and Epidemiology.

9 DR. PLATT: I am Richard Platt at
10 Harvard Medical School and Harvard Pilgrim
11 Healthcare.

12 DR. LACEY: I'm Gary Lacey from
13 the Therapeutic Goods Administration in
14 Australia, the national drug regulator of
15 Australia.

16 DR. GOGOLAK: Victor Gogolak,
17 DrugLogic. I also work with the University of
18 Maryland in drug safety.

19 DR. KRAMER: I'm Judith Kramer,
20 Duke University. I'm an investigator for the
21 Duke Center for Education and Research on
22 Therapeutics, and I've just been named the

1 Executive Director of the -- something called
2 the Clinical Trials Transformation Initiative,
3 which is a public/private partnership with FDA
4 and, hopefully, all stakeholders to see if we
5 can improve the way we do clinical trials.

6 DR. WOLFE: Sid Wolfe, public
7 citizen, Health Research Group in Washington.

8 DR. MCGLEW: John McGlew with the
9 American College of Clinical Pharmacy.

10 DR. DAI: Waju Dai, Sanofi
11 Aventis.

12 DR. TRONTELL: Anne Trontell,
13 Agency for Healthcare Research and Quality
14 where I am the program director for the
15 Centers for Education, Research and
16 Therapeutics.

17 DR. CUNNINGHAM: Fran Cunningham,
18 Director for the Center of Medication Safety
19 at the Department of Veteran Affairs.

20 DR. KOTSANOS: Jim Kotsanos in the
21 Global Patient Safety Organization at Eli
22 Lilly and Company.

1 DR. DIEK: Gretchen Diek, Safety
2 and Risk Management, Pfizer.

3 DR. DAL PAN: Gerald Dal Pan,
4 Surveillance and Epidemiology, FDA.

5 DR. IYASU: Okay. This session in
6 the afternoon is going to be probably harder
7 than the morning, because this is really about
8 time to answer -- sort of come up with
9 proposed approach for how we are going to
10 undertake this evaluation, which is really an
11 enormous effort and which would require, I
12 guess, several -- a couple of years or three
13 years to undertake.

14 For those of you who participated
15 in the panel in the morning, if we have time
16 after this panel is done, we might actually
17 ask you to also comment on the afternoon's
18 panel discussion. So please stick around, if
19 you are not in a hurry to take a flight or you
20 have other commitments.

21 So the question that needs to be
22 addressed in the afternoon is really a

1 discussion and a brainstorming on what the
2 research approach would be to answer the key
3 questions that were discussed this morning,
4 key questions -- We talked about the six
5 questions, but also there were a number of
6 amplifications and also new questions that
7 were discussed and suggested by the panel.

8 I think in that greater frame of
9 the question, it is really a public health
10 evaluation of the value and the value of the
11 spontaneous adverse event reports, and you
12 could frame it in various ways. But I think
13 the key question is, looking at it from a
14 public health perspective, to me, talking
15 about it in terms of public health perspective
16 or patient perspective is really, more or
17 less, the same.

18 So that is where the framework is.
19 So in terms of the questions that we have,
20 what kind of design would be possible to
21 evaluate the system? What would be the data
22 sources that we need to look at? What would

1 be the outcome measures that we need to be
2 measuring, whether you are thinking in terms
3 of whether this is an effort that is a
4 descriptive approach or whether it is an
5 analytic project, whether it encompasses
6 qualitative as well as quantitative sort of
7 evaluation.

8 I want to hear more on all these
9 aspects in terms of the key questions that we
10 have, what the hypothesis would be. So I am
11 looking for a very rich sort of discussion on
12 these issues.

13 So I would open it up, and if
14 somebody wants to take the first -- Yes?

15 DR. PLATT: So I am unable to
16 participate in a large --

17 DR. STAFFA: I'm sorry, Rich, but
18 for the transcriber --

19 DR. PLATT: Richard Platt
20 speaking. I heard part of this morning's
21 discussion, but had to miss big pieces of it.
22 So forgive me if I cover some old ground.

1 I'll start with the premise that
2 we need an active surveillance system, but
3 it's not clear that we need the active
4 surveillance system we have. I say that for
5 a variety of reasons -- I'm sorry, the passive
6 surveillance system. Okay, backing up.

7 We need a passive surveillance
8 system, but it's not clear we need the one
9 that we have, because there are a number of
10 things that are changing very rapidly that are
11 almost certainly going to be important
12 fixtures in the health care landscape that I
13 think would have an important bearing on what
14 we would want from a passive surveillance
15 system.

16 Specifically, it is very likely
17 that there is going to be a much more robust
18 active surveillance system, and it is very
19 likely that we are going to have much better
20 ways of communicating with clinicians and with
21 patients.

22 In that context, it seems to me

1 that much of what we have relied on a passive
2 surveillance system for is likely not to be
3 especially helpful. So I'll give two
4 examples.

5 I did hear several speakers this
6 morning say we need background rates, and I
7 agree with that, but that is going to come out
8 of active surveillance systems, I think.

9 We certainly need clinicians --
10 What I think we need from clinicians is their
11 informed judgment about attribution. Do they
12 think that an outcome is plausibly related to
13 an exposure.

14 I think that's among the most
15 valuable things we get from a passive
16 surveillance system, but I would substitute
17 the notion of, instead of true spontaneous
18 reporting, I think we could talk about
19 elicited surveillance in which we use a
20 variety of automated methods to identify
21 outcomes that are not known or expected
22 results of exposures to therapeutic agents and

1 query clinicians about whether -- about their
2 judgment about whether this is an adverse
3 event or not, and whether or not they think it
4 ought to be reported.

5 So there -- and I think we could,
6 similarly, do the same kinds of things with
7 many people who are exposed to the drugs. It
8 is entirely possible with the communications
9 tools that we have now to build a system that
10 essentially enrolls a cohort at the time that
11 drugs are dispensed and provides easy ways for
12 them to do reporting.

13 It would be entirely different
14 from the surveillance system that we use now.
15 That's a long run-in to say I'm not sure these
16 are the right questions for us to be dealing
17 with this afternoon.

18 I have real reservations about
19 encouraging FDA to embark on a very thorough
20 study of a system that we might be able to
21 decide could be substantially revamped and
22 that ought to be the basis for the agency's

1 serious consideration.

2 So I'll end this remark where I
3 started. I believe we absolutely need a
4 passive surveillance system, but we should be
5 thoughtful about what we want it to provide,
6 knowing that we are on the cusp of having much
7 better ways of getting much of the information
8 that we have had to rely on a passive
9 surveillance system to give us, and being
10 mindful of the opportunity costs of the FDA's
11 maintaining the passive surveillance system
12 that it currently has.

13 I know that it consumes a
14 substantial amount of the agency's resources,
15 and I think that FDA needs to be thoughtful
16 about what's the best use of the limited
17 resources that it has.

18 DR. IYASU: Anne?

19 DR. TRONTELL: I agree -- This is
20 Anne Trontell from AHRQ.

21 I agree with Rich that I do
22 believe the future will bring us better data

1 systems that would supplement and maybe even
2 ultimately serve to replace the passive
3 reporting system. But my sense -- and maybe
4 you can redirect me if my impression is wrong
5 -- is that we were largely focused on sort of
6 some of the specifics about the system that is
7 in existence today and how it might be made
8 improved or how its public health value, as
9 you stated, can be improved.

10 My question there is that the side
11 discussion, particularly if I'm going to start
12 thinking of studies and outcome measures to
13 assess whether or not value has been achieved,
14 I'd like to get maybe a little discussion
15 going about what we mean by value; because,
16 clearly, we all have as a common concern to
17 improve health outcomes in patients. But
18 there is a certain value in hypothesis
19 generation that, obviously, hinges on the
20 specificity and sensitivity of the method and
21 the costs that are incurred for different
22 forms of data collection, the nonserious

1 reports or the consumer reports.

2 Even using the method of labeling
3 actions as a metric of success has some
4 dissatisfaction, because you ultimately want
5 actionable information that a clinician or a
6 patient can use for deciding whether or not to
7 take a drug.

8 So I'd like to maybe ask your help
9 in making clear whether we should go broad or
10 narrow in terms of the comments we are
11 focusing on passive reporting today.

12 DR. IYASU: Let me just make a few
13 comments. At least from what we heard this
14 morning, there seemed to be some consensus
15 that passive surveillance or spontaneous
16 reporting per se is here to stay for sometime.
17 We are not ready to throw it out, and there
18 were many comments that were made by panel
19 members stating that -- its value, both from
20 the patient perspective as well as the
21 reporting community perspective.

22 There are certainly some areas

1 that have been suggested by panel members that
2 could actually benefit from a revamping
3 improvement in terms of stimulating adverse
4 event reports, in terms of communicating what
5 happens to the reports, and the safety issues
6 that may arise.

7 So there are a number of issues
8 that have been discussed this morning that
9 sort of give me some direction in terms of the
10 passive surveillance or spontaneous reporting
11 being there for sometime, if not for -- you
12 know, I don't know how long it would, but that
13 will be part of the question that will have to
14 be assessed.

15 We know active surveillance or
16 some variance of it is a very active area of
17 discussion right now, and it may possibly be
18 that those systems would bear some fruition in
19 the very short time, but still that's not yet
20 a reality. But I think yet there is
21 commitment to going toward that, but I don't
22 think that what we heard is replacing the

1 system by -- the existing spontaneous
2 reporting system by another system.

3 Do you want to add to that?

4 DR. STAFFA: Well, I agree. I
5 think -- I'm not sure what the future looks
6 like and exactly what passive surveillance
7 looks like. So I think you made a good point,
8 that we need to continue passive surveillance.

9 Whether it looks like what we have
10 now or not is up on the table, but as we move
11 toward active surveillance, which I think
12 everybody agrees that we need to be exploring
13 this -- and I think the agency as well as many
14 of you at the table are doing exactly this --
15 there is the issue of trying to understand
16 better what passive does, so that we then
17 understand what we can expect from active;
18 because I don't think they necessarily do the
19 same things, and I don't think we have ever
20 adequately addressed -- It's long overdue.

21 We probably should have done this
22 kind of look at passive surveillance a long

1 time ago, but there was not the opportunity or
2 the funding to do so, and now there is.

3 DR. KOTSANOS: Jim Kotsanos.
4 Building on that -- I don't want to dig into
5 that particular question, but I thought this
6 study that was presented today that was
7 undertaken by the FDA and shared was a good
8 start.

9 It, you know, identified at least
10 a targeted outcome that was attempting to
11 understand the contribution that spontaneous
12 reports could make to looking at safety
13 related actions.

14 Quite frankly, if we were to build
15 on that type of approach, I think we could
16 more fully explore a number of the questions
17 that you have outlined in 1 through 5.

18 So if we had an outcome defined as
19 safety related actions, whether they be
20 letters from FDA to sponsors or whether they
21 be changes to the warning section -- I mean,
22 there was a host of things that were presented

1 by Mara that could be identified along with a
2 look at a host of questions, whether they be,
3 you know, did the initial safety signal come
4 from spontaneous reports or did they come from
5 clinical trials? If they were spontaneous
6 reports, were they driven by consumer reports
7 or was it health care professionals?

8 So in a way, when I read the
9 questions and then saw the presentation, it
10 fit together very nicely that that would be a
11 good platform to build from.

12 Of course, the key thing, I think,
13 methodologically is one would have to just
14 drill down into those data sources to see
15 where that initial safety signal came.

16 I think, Solomon, you said it
17 earlier. The data are very dispersed, and
18 it's just going to require hunting for it, and
19 somebody from the audience even indicated
20 that, you know, institutional memory needs to
21 be tapped. Maybe that institutional memory
22 exists outside of the FDA, at the sponsor

1 companies or elsewhere.

2 DR. IYASU: Okay.

3 DR. KRAMER: I'm Judith Kramer. A
4 number of years ago the Centers for Education
5 and Research on Therapeutics had a series of
6 think tank meetings on both risk assessment,
7 benefit assessment, risk management.

8 In the process of having this
9 discussion about risk assessment, the same
10 question was posed: What is the cost to the
11 system of addressing spontaneous reports in
12 the way that we are currently doing it?

13 Of course, hidden in there was
14 also, well, what does it produce. But we
15 decided to go down the path of documenting
16 cost, which we did, and there is a paper
17 published in Health Affairs that did that.

18 Of course, we did the easy part,
19 which was how much resources are people
20 putting to it. But we are now talking about
21 the hard part.

22 Before we go digging again into

1 study designs to address these specific
2 questions, I would like for us to think about
3 whether or not the amount of effort that we
4 would be putting to this is really where we
5 should be putting our effort, as Rich pointed
6 out.

7 I personally was really struck
8 with the question that June Raine asked this
9 morning when she said, well -- asked about the
10 metrics we have for our system. I think we
11 would go a long way to have some information
12 on our system if we were literally just
13 systematically, prospectively collecting
14 information about how many -- well, first the
15 fund signal, then how many signals are we
16 generating, how many regulatory actions.

17 I need some clarification for my
18 own thinking about these questions to
19 understand how accessible this information is.
20 For instance, regulatory action taken: Is
21 there any link between that regulatory action
22 and a documentation of what the sources or the

1 initial sources for that information are, or
2 is it literally a digging exercise, as Jim had
3 pointed out?

4 So it would help me in thinking
5 about it if you could at least clarify that.

6 DR. DAL PAN: All right. So every
7 regulatory action has a letter to the company
8 to document that action. So for something
9 like the labeling change, that's usually in
10 response to a submission from the company
11 which may have some of that information in it
12 that leads to the change.

13 Then there are also internal FDA
14 reviews that relate to that, that you have to
15 actually go look for. Since 2000 onward,
16 those reviews are in an electronic archive
17 system. Prior to 2000, they are largely in
18 paper based jackets that fill a room many
19 times the size of this one.

20 There is no database, though, that
21 says this label action was taken on this day,
22 the source of the data was spontaneous data,

1 clinical trial, pharmacology study. That kind
2 of database does not exist. We would have
3 presented that, if it did.

4 So to some degree, there is a
5 digging feature to that. You can usually get
6 to the bottom of it, but it does take a lot of
7 work to do it.

8 DR. DIEK: Gretchen Diek, Pfizer.

9 I would agree with that. Many
10 companies also keep records of what data they
11 look through to suggest a labeling change or
12 to have in preparation for conversations with
13 the agency as well.

14 I do agree, in some instances more
15 recently some of that information may be more
16 readily available than older information, and
17 I think it is something that can be gathered.
18 And if you ask the question in a certain way,
19 if you can just have basic blocks, is this a
20 spontaneous report, is it from review of
21 spontaneous reports, was it from an
22 epidemiological study and so forth, I think

1 that companies would be able to provide that
2 sort of information.

3 I don't think it is anymore
4 onerous than -- and I say this. It can be
5 onerous going through a medical chart, but I
6 do think we have this tool that's getting
7 larger and larger and larger and larger, and
8 we are collecting these data forever, for the
9 life of a product.

10 At some point, the question -- I
11 mean, it's a reasonable question to say all
12 the FDA's resources are being put to this, and
13 all of industry's resources being put to it.
14 Is that being well spent for patient safety?
15 Are we really getting information that helps
16 physicians prescribe the drug by collecting
17 all this information, reviewing all this
18 information, and so forth?

19 So it's a scientific question. I
20 think it's worth using. I think the passive
21 system is going to be around for a long time,
22 and it is reasonable to say let's try and

1 refine it as best we can.

2 If it's most useful within the
3 first seven to 10 years of a drug's life, then
4 let's focus in on that. Let's collect the
5 types of data that we feel will be useful.

6 DR. WOLFE: In your opening
7 statement this morning, Solomon, you said
8 something that is at least at the core of my
9 interest in participating in this, which was
10 we need an optimal tracking of decision
11 making, and that is what is, I think, missing.

12 Our frequent and seemingly
13 unending criticism of this or that drug is
14 really based on looking at data rarely from a
15 randomized trial but accumulating data on
16 hepatotoxicity or whatever and saying it looks
17 as though there are enough cases that clearly
18 don't have any other explanation; the drug
19 does not have any unique benefit that would be
20 a countervailing force; why isn't this drug
21 being taken off the market. And we will
22 frequently petition for it.

1 I think that, if one went back, as
2 Ralph Edwards suggested briefly this morning,
3 and really did a serious post-mortem -- and I
4 think that that could be the subject of an
5 RFP. You have 20 drugs or whatever it is that
6 have been taken off the market in the last 10
7 years.

8 We did a study which was mentioned
9 by Mara this morning. It was published in the
10 JAMA a few years ago. We looked at every drug
11 approved for a 25-year interval in the United
12 States, and the research question was: What
13 are the odds that a drug is going to either be
14 taken off the market -- in a smaller number of
15 instance -- or be the subject of a black box
16 warning?

17 The answer was about one out of
18 five drugs in a 25-year period were going to
19 be subject to one of those. And consistent
20 with what Mara showed this morning, it keeps
21 going on, but the slope of the curve in a
22 Kaplan-Meier curve was much sharper in the

1 first two years for withdrawals. Half of the
2 drugs were withdrawn within the first two
3 years, and half of the drugs were subject to
4 a black box warning in the first seven years.

5 In looking back at the withdrawals
6 again, I think that there is a huge amount of
7 information that is available, both in animal
8 pharmacology studies -- and I'll mention one
9 example in a second -- and in adverse reaction
10 reports, because that is, again as I mentioned
11 earlier, the main basis for drugs being taken
12 off the market in any country that has any
13 kind of regulatory scheme. It's purely
14 adverse reaction reports or sometimes
15 augmented by something else.

16 Companies have a requirement,
17 which I strongly support that they have, to do
18 animal studies. Just an example of
19 extraordinary for me, because I look at a lot
20 of these animal data, the whole family of so
21 called glitazones -- troglitazone,
22 rosiglitazone, pioglitazone -- had what in my

1 view were sort of unprecedented cardiac
2 toxicity showing up in the animal studies, and
3 often at not very high doses.

4 So I would say part of thinking
5 about a research proposal is to look backward
6 at the animal data. The signals from
7 randomized trials began with troglitazone.
8 There was a strong signal there wasn't paid
9 enough attention to of just huge elevations in
10 liver chemistries, formerly called liver
11 function studies, and see which of those was
12 contributing, which one was not paid attention
13 to; because I think that there are enough
14 examples where one or two or three or four
15 years went by between a time when reasonable
16 people would agree there was enough of a
17 warning signal that something wasn't done.

18 So your suggestion about tracking
19 decision making, not just to parse it out as
20 other people have said. Is it the adverse
21 reaction reports? Is it, in the rare case of
22 a Vioxx, randomized controlled trials, two of

1 them? Is it a combination of that and signals
2 that came off from the animal studies?

3 I think this would be a very
4 useful study as long as the people who were
5 doing it had access to memos and internal
6 documents that we in the public don't have
7 access to.

8 Maybe I can get back to this other
9 idea later, just on collecting better data on
10 adverse reactions.

11 DR. IYASU: Okay. Thanks. Jim,
12 hold that thought. I wanted to sort of get
13 some more discussion on the issue of trying to
14 focus it. I think one area of focus that
15 Sidney is talking about is the possible area
16 of withdrawal. But that is an area that has
17 been looked at before.

18 How much -- I want to hear from
19 other folks about how much useful additional
20 information we can get by focusing on
21 withdrawals and also on the other issues that
22 he talked. Is that a possible avenue for

1 inquiry that we are doing?

2 DR. DIEK: Gretchen Diek from
3 Pfizer.

4 Well, sometimes we are still
5 required to send in adverse events on drugs
6 that have been withdrawn. So I guess the
7 question is: Is that information -- It may be
8 information for -- useful information for
9 making further decisions, but is that
10 information that's used for patient safety?
11 So I am throwing that out as a question.

12 DR. EDWARDS: Ralph Edwards.

13 I think, if we are going down the
14 track of talking about this kind of area that
15 Sidney Wolfe has started us on, what we need
16 to do is to find out at each point what
17 decisions were made and why they were made and
18 on what evidence, because we start off with
19 spontaneous reports. And as I said this
20 morning -- or often anyway -- we then say,
21 okay, this looks like a signal and, therefore,
22 we will take it to the next step, or this

1 isn't a signal, this is spurious.

2 I want to know how it is that
3 those decisions are made, what are the factors
4 that take us from one step to the next, and
5 why, and with what outcome. But I didn't
6 think that that was the main purpose of where
7 we are. I thought we were going to discuss
8 these six questions, and very much relate them
9 to our spontaneous reporting system as we
10 have it now.

11 Whilst I've got the microphone, I
12 think I'd like to comment on Richard Platt and
13 say that I don't think that we have the
14 evidence that says the spontaneous reporting
15 system is bad news and won't be good in the
16 future. The evidence simply isn't there.

17 There is a British saying -- I
18 don't know whether it's here -- if it ain't
19 broke, don't fix it. So I think we need to
20 find out whether our system is broke, isn't
21 fit for purpose, or not -- best fit for
22 purpose, and we need data in which to do that.

1 I thought that is where we were
2 heading this afternoon, to try to get that
3 data to tell us where we were.

4 DR. PLATT: I didn't mean to imply
5 that the system isn't useful at all, but I
6 think that many of the things we have made it
7 be useful for will be better served in other
8 ways.

9 So my hope is that the FDA skates
10 to where the puck will be, not to where it is
11 right now. That is my concern in listening to
12 the way these questions have been set up, is
13 that you will study the passive surveillance
14 system as it has been for the last 20 years or
15 the last 10 years, and I'm pretty confident
16 that by the time you finish that evaluation,
17 you won't -- we won't be living in that
18 environment, and you won't be well positioned
19 to ask what can the passive surveillance
20 system contribute in the new situation that
21 FDA finds itself.

22 So I think that there is a

1 considerable amount of additional discussion
2 and qualitative work to say posit this kind of
3 an environment, what can passive surveillance
4 contribute, and how can we ascertain -- how
5 can we learn from the system we have, whether
6 it can serve those purposes well, and how we
7 can be positioned to allow passive
8 surveillance to be an important complement to
9 the other kinds of systems that are emerging
10 already. That is not a dream that we are
11 talking about.

12 DR. IYASU: I think, Rich, you
13 just sort of touched upon a very important
14 point here, I think. what he said about the
15 passive system being a complement to what
16 might emerge as a bigger or more fruitful
17 effort in the future.

18 I think that is where we are going
19 with this, and I think several people have
20 expressed their opinion this morning saying
21 that, as we revamp our drug safety system,
22 where do we see the role of spontaneous

1 reporting as we emerge into this sort of
2 uncharted territory.

3 DR. PLATT: Well, so I'll be more
4 specific then about what spontaneous passive
5 reporting system you are asking for advice
6 about evaluation, because it seems to me that
7 substantial parts of the system as we know it
8 are very unlikely to be helpful.

9 It may be that, if you frame the
10 question in a certain way, you would get
11 something close to a consensus saying we can
12 put those questions aside, even though you
13 could ask them about the system as it is now.

14 So I just want to make sure that,
15 as FDA thinks about how to deploy its
16 resources and what it wants to ask about, that
17 it does the right thing. I just think that --
18 For instance, I think it would be a mistake to
19 say how can we improve the passive
20 surveillance system so we have a better idea
21 whether there is an increased rate of
22 reporting compared to baseline. I mean,

1 that's just a very difficult thing to do, and
2 there will probably be better ways to get at
3 that.

4 Maybe everybody says, nope, we
5 ought to tackle that system, but --

6 DR. IYASU: Let me ask folks along
7 the same lines.

8 DR. TRONTELL: Just to build upon
9 Rich says, because I do like the idea of being
10 prospective looking as well as looking back
11 historically.

12 I think in certain clinical
13 conditions it may even be some expert group or
14 even a review of the data that is in existence
15 that might look to those events which appear
16 to be detected uniquely or preferentially with
17 the spontaneous reporting system:

18 Anaphylaxis, for example, or some of the
19 things where people tend to think drug right
20 away, Stevens Johnson and other phenomena.

21 It is probably few systems will
22 meet the passive or spontaneous reporting

1 system for that. Prospectively, I think in
2 anticipation of some of the regulatory changes
3 that FDA may face with the 1-800 number, you
4 may also have an ability to look prospectively
5 to see to what extent changes in the relative
6 percentage of consumer reports that you
7 receive and the potential value that you might
8 receive from those would be very valuable.

9 Picking up on a comment from Paul
10 Stang this morning, also to look at which
11 reports tend to be most actionable by safety
12 evaluators. So that, you know, a report that
13 is little more than a suggestion of something,
14 a few pieces of data -- you know, there may be
15 some, again, criteria where you may be able to
16 deburden the current system, which I don't
17 think anyone plans to replace in the near
18 future, to free up resources to consider some
19 of these active surveillance and other
20 options.

21 DR. DAI: Sorry. Waju Dai.

22 I was going to echo what Anne

1 Trontell just said. I think there are
2 information you can get retrospectively, and
3 there are information you just can't. We said
4 before not all data in one place can be easily
5 used to study even for addressing drug safety
6 signals, no matter how much I'd like to use it
7 as a basis to address them.

8 Sometimes, the information is just
9 not there. You couldn't possibly do that. So
10 for example, like this situation about
11 analysis we heard this morning -- I'm not sure
12 labeling change is the time that really the
13 signal is detected. Usually, probably
14 sometime ago. So probably spontaneous reports
15 was good enough sometime ago before the
16 labeling change was made.

17 So that's the time probably as
18 used spontaneous reports, and maybe after a
19 certain time, even labeling change occurs
20 later, there is no further information added
21 on.

22 So I think this kind of

1 information is not something you can just use
2 retrospective data. You probably need to dig
3 into more of individual case and have a
4 prospective study design to determine what
5 data elements you need to capture to help you
6 evaluate what really spontaneous report can
7 help us.

8 So I do agree with Richard about
9 this resources used in spontaneous reports
10 seems to be more than we really like to spend.
11 For example, like for serious reports I can
12 imagine you want to spend lots of resources
13 digging into information follow-up, but it
14 takes a lot of resources to do follow-up, and
15 for other types of reports it is probably not
16 necessary to have such a detailed follow-up,
17 but to what extent this can be stopped, I
18 think sometimes the prospective design would
19 help us better.

20 DR. IYASU: Could I go through
21 this section? Jim, I think -- or John.

22 DR. MCGLEW: Yes, John McGlew with

1 ACCP, American College of Clinical Pharmacy.

2 Following on from your comment, it
3 seems to me that there may be some value in
4 taking -- with reference to the U.K. model
5 that was made this morning with a adverse drug
6 reaction and the kind of implied causality
7 there, you know, we seem to have, obviously,
8 challenge with the volume of data we have and
9 our ability to analyze it and use it
10 effectively.

11 It seems that, if we could focus
12 on specific drug interactions as opposed to
13 human errors, prescribing errors, or problems
14 kind of at the human level, and not to
15 disregard them but just to distinguish the
16 two, you know, we could potentially kind of
17 cut down the volume of data we are collecting
18 and be able to analyze it more efficiently.

19 DR. GOGOLAK: Vic Gogolak,
20 DrugLogic.

21 I was just thinking that, you
22 know, I have always looked at spontaneous

1 reporting or whatever we want to call it as a
2 complement. I mean, we have animal studies
3 for really gross problems, and we have the
4 clinical trials to form the baseline of the
5 behavior in some reasonable population,
6 depending on the population we are targeting
7 the drug for. But in my mind, it was always
8 the surprise aspect, either a surprise in
9 compliance, in polypharmacy, in a reaction, in
10 a genotype or whatever. It could be due to
11 diet.

12 We see all sorts of interactions.
13 So the value of whatever you want to call it,
14 spontaneous always seems to be there. I don't
15 want to just pile on the argument for
16 spontaneous reporting, but I think the
17 characteristic -- and somebody started the
18 discussion saying we need to look at the value
19 of all of these systems and bridge from this
20 abstract value to something concrete we should
21 dos.

22 That wa the important part of our

1 study this morning. Even though it was just
2 the beginning, it made the link between things
3 that happened and actions.

4 I think, not to trivialize it, but
5 if we could get a simple list of things we
6 expect the spontaneous system to do and
7 improve on, that list will improve over time.
8 the researchers will have a chance to think
9 about it.

10 A couple come to mind. For
11 instance, reactions that might not have been
12 seen because of technology, maybe of
13 specialists that are looking at something in
14 cardiology or oncology, that they can find
15 earlier. So now they are going to report it.

16 A simpler thing is a drug-drug
17 interaction. In other words, if you have
18 somebody, a million people, million
19 prescriptions of one drug, but you have maybe
20 only 1,000 or 2,000 of them taking a
21 particular concomitant with not even a
22 relatively rare but, let's say, an infrequent

1 reaction, you are going to have something that
2 is going to require spontaneous reporting.
3 You will never have any kind of cohort study
4 that will look at millions of people.

5 So if we get that list of things
6 that we'd like -- for instance, compliance,
7 you know, what are people doing that might
8 make this drug work wrong, what populations
9 could it be misused in -- and there's evidence
10 in history.

11 That's why I think the real value
12 of looking back at these actions to say, well,
13 not exactly what the histogram is but what is
14 that list, then we could look at the
15 mechanisms and ask these researchers, well,
16 now go quantify it. What more do we have to
17 know? Do we have to have better ways of
18 recording concomitant drugs? Do we have to
19 have a population of people to go back to?

20 I'll give you another example,
21 launch. You know, You're coming out of a
22 clinical trial. You are targeting 5 million

1 prescriptions, and we know, as we have seen
2 for many drugs -- for instance, in Viagra and
3 all of the stuff that hits the front page of
4 the Washington Post, and I live here locally;
5 it hits the front page of the New York Times
6 maybe only once a week, but there is something
7 almost daily in the Washington Post about drug
8 safety, and all of those things are clear, but
9 not all of them are well thought out.

10 We say, well, we didn't know about
11 it or it was a surprise. So maybe during
12 launch there are other pieces of information.
13 So I think it's going to be a continuum from
14 cohort studies in clinical trials to drugs
15 that are on the market for maybe five or 10
16 years, and you can't afford to study but you
17 say, well, keep a system out there looking,
18 and maybe in that first three years to do a
19 very clever combination.

20 I would almost love to see that
21 natural dovetailing. I saw it this morning
22 where you say, hey, let's get those nonserious

1 for the first three years, but after we
2 understand that, we probably have enough data
3 to play with to see if there is something
4 small there, and then we can reduce the
5 burden.

6 So you know, that's -- Bottom line
7 what I'm saying is that it would be good if
8 this panel could come out with a very specific
9 list of recommendations for the FDA to have
10 these researchers investigate.

11 DR. IYASU: I think that is
12 excellent comment. I think, along those
13 lines, I think if we could continue some more
14 discussion in terms of the specifics or
15 outcome issues that we need to look at, I
16 think that would be helpful. That's what we
17 are looking for, really, to try to maximize or
18 to increase the utility of spontaneous reports
19 in patient safety. What is it that we need to
20 look at or ask the researchers to look at?

21 I think framing it that way would
22 be very helpful. So if you could sort of

1 continue along the same lines, that would be
2 really helpful.

3 DR. DIEK: Gretchen Diek from
4 Pfizer.

5 I wanted to get back to Waju's
6 issue about prospective versus retrospective
7 design. I think, if you were trying to look
8 at issues of timing and, as you said, not
9 looking at the labeling change per se or the
10 action, but when the signal is first detected,
11 I agree that prospective design would probably
12 be better. But I don't know that that is what
13 we are looking for here.

14 We are looking for some proxy that
15 a safety decision was identified and the
16 decision was made -- or a signal was
17 identified and some decision was made. I
18 think you can do that retrospectively, and I
19 think we saw that this morning.

20 So i go back to what Jim had
21 suggested earlier, that we look at that study
22 that was carried out and told to us this

1 morning and see what else we can mine from
2 that to answer some of these questions.

3 Do we have information on the
4 source of the signal or the source of the
5 information? Can we get that information?

6 I think that, if you see what you
7 can really get out of that study, that will
8 tell you how you need to frame the RFP going
9 forward to fill in additional blanks.

10 DR. CUNNINGHAM: Fran Cunningham,
11 Department of Veteran Affairs.

12 I think I would like to comment on
13 one thing that was already said, and that was
14 using what you already have for known events,
15 drug-drug interaction that was just mentioned.

16 I've looked at things that came
17 out probably years later that was already in
18 your database, statins and fibrates, and when
19 you probably were already seeing signals for
20 myopathies and rhabdo, and we found out years
21 later that it was a combination of the doses
22 of the drugs that were used.

1 That's something that sits in the
2 database that you could evaluate, specifying
3 specifics, knowing what the underlying
4 mechanism of action is for certain agents or
5 picking up a rare event that you were able to
6 pick up, such as rhabdo, and seeing the
7 combination of products that caused it. That
8 information could be investigated further.

9 I think a second thing that could
10 be looked at is, again from a public health
11 standpoint, as you see AEs constantly reported
12 back serious and you evaluate and you see that
13 it is really related potentially to the dose
14 of the agent, and that could be a public
15 health warning coming back in a "Dear
16 Provider" letter or a "Dear Practitioner"
17 letter: This drug is constantly being
18 prescribed at a dose higher than recommended;
19 if you use it at a dose lower, you should not
20 see A, B and C.

21 So you can constantly mine your
22 data as it is now to see how your AEs are

1 occurring. Are they occurring because of
2 dose, potentially? Are they occurring because
3 of underlying organ failure, potentially, and
4 how the agents are being used?

5 DR. KRAMER: Judith Kramer.

6 One of the things that bothers me
7 as we talk about how to design the research is
8 this. The research question seemed to assume
9 that we have a uniform situation.

10 I mean, if you are talking about
11 safety issue identification and time to
12 identify it, it is going to vary tremendously,
13 depending on all of the limitations that we
14 have listed of the passive surveillance
15 system.

16 I just want to make that point.
17 I'm not sure we are going to find sort of a
18 singular answer to any of these questions. So
19 I think we should maybe start from accepting
20 the complexity and qualifying what we should -
21 - what we could study.

22 A second point is I want to talk

1 about ways in which the ultimate safety
2 assessment system that we might have, which
3 would clearly involve some form of active
4 surveillance, could be complementary with a
5 passive surveillance system.

6 I would -- The one thing that
7 bothers me a lot about the idea of having
8 large distributed data networks as the only
9 source of safety surveillance is the issue
10 that, the way doctors report adverse events,
11 there are many things that aren't captured
12 with a ICD9 code, if we are using claims data,
13 for instance, in active surveillance systems.

14 You have to imagine how are we
15 going to get at this, and people talked about
16 electronic health records mining terms. But
17 maybe a way to approach this is to say, well,
18 what could we not get well from an active
19 surveillance system and, therefore, target our
20 spontaneous text reports where we get the raw
21 terms and the preferred terms.

22 On the other hand, we keep saying

1 how great the passive surveillance system is
2 for defining these rare events. Well, that's
3 because they are easy. If you see them, you
4 know they are rare, but it does not define a
5 causative mechanism. Right? We are still in
6 a conundrum when we see -- if we see one case
7 of Guillain-Barre, it's bad luck. If we see
8 two, your drug is dead.

9 We need to think about whether
10 those sorts of questions would be better
11 suited by the type of thing that Dr. Platt is
12 doing in his HMO research network and larger
13 health plan conglomerates addressing questions
14 of safety.

15 DR. IYASU: Thanks.

16 DR. DAI: Yes. I wanted to
17 comment on what Judy said. She said we should
18 find out what is not done well by a claims
19 database, but I think the other way is what is
20 not done well also by spontaneous reports.
21 Both are basically complementary to each
22 other.

1 When I said that we need to find
2 out early time before the action for labeling
3 change, I meant usually a signal you do
4 confirm with deepened data sources. It is
5 very difficult to piece out one has more
6 important role than the other one without
7 doing it prospectively.

8 That's what I meant earlier, that
9 it is not the time for you make labeling
10 change is the time, but the time earlier when
11 you are thinking about starting doing actions
12 of digging into active surveillance system
13 claims database and what was the source of
14 information make you do that.

15 I wanted to also comment on the --
16 Definitely there are a lot of things we can do
17 with retrospective study design, and
18 specifically back to what was discussed
19 earlier today with the presentation on the
20 signals detected.

21 You know, I keep on thinking that,
22 yes, there are signals across the years, seems

1 to be equally across the years, but the
2 important thing is are they important adverse
3 events detected later on, you know, five or 10
4 years at marketing.

5 You know, there are many labeling
6 changes. Maybe some are very minor. It makes
7 no difference to the public health at all.
8 Also, whether these adverse events actually
9 could be probably better addressed by, say,
10 claims database or ultimately to the medical
11 records.

12 So those are the questions I would
13 raise for future research.

14 DR. PLATT: Could I just insert a
15 comment? I'm a little concerned about sort of
16 the notion of a duality that we are talking
17 about, that is, we either use an active
18 surveillance system or we use something like
19 our existing passive system; because I don't
20 think that's the only future we have.

21 For instance, in an environment
22 where already a sufficient number of

1 clinicians use electronic medical records, it
2 would be entirely feasible to look at new
3 diagnoses and ping the physician or the
4 provider and say your patient has been -- is
5 being treated with these agents, and there is
6 a new diagnosis that might be an adverse
7 reaction; do you think it might be? If so,
8 press Enter and you can submit a report to the
9 FDA. It's pre-populated with everything
10 except the field that says, clinician, what do
11 you think?

12 Now I don't think that's the
13 passive surveillance system we've been talking
14 about, but it's the one we might have, and we
15 would study it entirely differently.

16 So I'll keep saying, I have grave
17 reservations about your studying the system
18 that we have, partly because we've all been
19 describing something different about passive
20 surveillance, and partly because I think that
21 much of you might get as an answer is
22 something that won't be of interest to us.

1 DR. IYASU: Well, I think that one
2 viewpoint. So we will just have other
3 viewpoints, I guess, from this side of the
4 table.

5 DR. EDWARDS: I'm losing it, I
6 think. This is beginning to sound like a kind
7 of the stuff that in Europe we hear about
8 education, that someone says, oh, well, the
9 education system is terrible, it needs
10 changing in this way; and we don't have the
11 metrics from the old system to know whether
12 the new system is any better.

13 I think that's where we are very
14 much with pharmacovigilance. We don't
15 actually have good metrics. One of the
16 wonderful things, the opportunity that we are
17 being presented with here, is to get some
18 metrics.

19 I mean, I take your point,
20 Richard. Looking way back at the system as it
21 was historically may not help us very much,
22 but we had a demonstration today of looking at

1 possible trends. You know, how is the system
2 behaving over a period of time?

3 What we need to decide is what are
4 the key metrics that we want to measure, and
5 at the same time decide what it is we want out
6 of the system. And by the way, we need some
7 definitions. We need to know what a signal
8 is. We need also to be sure that, since we
9 are using databases, that the quality of those
10 databases, the way in which disease is entered
11 into the databases and terminologies,. All of
12 that we need to look at.

13 I think just posing new questions
14 and possible new ways forward without those
15 basic metrics is going to be a mistake.

16 DR. IYASU: Okay. Gary? Can you
17 state your name?

18 DR. LACEY: Yes. Gary Lacey,
19 Therapeutic Goods Administration.

20 Yes, I would just like to agree
21 with what Ralph Edwards was just saying, in
22 that we need to know what it is we are

1 measuring within the spontaneous adverse event
2 reporting system, because as certainly the TGA
3 and, I know, the FDA and in Europe we are
4 moving toward a more active surveillance
5 system. We don't have the metrics from the
6 active surveillance system yet, and if we are
7 going to compare whether the new active system
8 is giving us greater utility, greater benefits
9 to public health, greater benefits to patient
10 health, we need something to compare that to.

11 At the moment, we've got the
12 spontaneous adverse event reporting systems in
13 various countries, but we can't compare them,
14 because we don't know exactly what it is we
15 are looking at, and it is very important that
16 we have been given this opportunity to say
17 what is it we are looking at in the
18 spontaneous adverse event reporting systems so
19 that we can compare now and into the future as
20 we move forward.

21 DR. IYASU: Anne?

22 DR. TRONTELL: I do think it would

1 be beneficial -- perhaps we can't do it today
2 -- to have some better definition of what
3 constitutes a signal. My own experience is
4 that, you know, there's probably some gradient
5 of progression from a worry, you know, one
6 case of pancreatitis when you suddenly say --
7 A case series will be assembled, perhaps even
8 FDA's own internal time frame in which one of
9 its safety evaluator staff makes that step
10 might be the point where it has reached a
11 level that FDA personnel effort at least has
12 been expended and presumably a further
13 discussion and march down the road to whether
14 or not further action needs to be taken.

15 I do completely agree that the
16 analysis we saw this morning from Mara was
17 very helpful, and I think some refinement of
18 that, with some particular attention to the
19 areas where some of us may presume there is
20 potential efficiencies to be gained, in the
21 area of nonserious reports or in the area of
22 consumer reports where, again, the -- not that

1 these would ever be dismissed, but the extent
2 of follow-up action required on the part of
3 FDA or industry might be somehow tempered,
4 could be directed toward other events that
5 might be more useful or meaningful. But the
6 signal definition process is probably
7 something, as others have said, that we really
8 need to have as our starting point.

9 In my own experience at FDA, this
10 is an iterative discussion. No one really
11 drops the flag and says I plant my flag here,
12 I'm the first one to declare the signal;
13 because, in fact, it's often a dialogue.

14 DR. IYASU: You are absolutely
15 right. It is a continuum in terms of the
16 evaluation process, and decisions, interim
17 decisions, have been made at each point,
18 sometimes not very well defined. But then the
19 threshold that one reaches to go to the next
20 step may be looking at a case series or going
21 to other databases.

22 Those sort of points, decisional

1 points, you know, the thresholds, the
2 criteria, may defer depending on what the drug
3 is, what the condition we are looking. So I
4 don't know whether there is one metric, but I
5 think certainly looking for the triggers
6 process, what triggers a decision to go
7 forward or not forward, whether we determine
8 early on this is a false positive signal or
9 not or when do we do it, you know -- is it
10 later, is it early, what really drives that
11 decision process -- those are all very
12 pertinent questions.

13 I think one of the things that we
14 need to address probably in this effort is
15 just to look into those metrics.

16 All right, Judith.

17 DR. KRAMER: Just one comment on
18 that. I wonder -- It would be interesting to
19 see how uniform that decision is across
20 different reviewers. I mean, there are a lot
21 of factors. There are drugs, but there's that
22 subjective element in terms of how

1 aggressively an individual would pursue
2 something or their threshold for concern.

3 So that would be interesting.

4 It's combining social sciences with a
5 different type of science, but it would be
6 interesting.

7 DR. STAFFA: Being the bad cop to
8 Solomon's good cop, what I'm hearing a little
9 bit here is -- I'm intrigued by the
10 prospective versus retrospective pieces here,
11 and what I'm hearing is that maybe
12 retrospectively, to a certain degree, not into
13 the deep, dark recesses of history but recent
14 history to understand more about regulatory
15 actions, as we have done with Mara's work to
16 start, and to continue to build on that is
17 useful. But then to look at the decision
18 making process, given the newer systems of
19 collection of decision making information --
20 that piece might be more effectively done
21 prospectively.

22 I can tell you, as we sat down to

1 formulate Mara's work, we could argue all day
2 about what a signal is, but it was a lot
3 easier to decide on what a regulatory action
4 is. So in retrospect, that may be the more
5 difficult animal to tackle; whereas,
6 prospectively maybe we gain information on
7 that and come to consensus on that.

8 I was wondering if folks had other
9 comments on kind of dividing things that way?

10 DR. KRAMER: Could you clarify
11 what is in Judy Racoosin's new system that she
12 described? Is that work what you would be
13 accessing prospectively?

14 DR. DAL PAN: Is Judy here? No.
15 Paul Seligman? Is he here? He was here.
16 Okay.

17 Well, what she is describing,
18 really, is a database that will be used to
19 track safety issues and to track the
20 assignments, the work and the reviews as well.
21 Previously, those things had been unlinked --
22 hadn't been linked to each other. So amongst

1 other things it will be a system to track
2 safety issues, when they were identified, who
3 is working on them, the status and then when
4 they are closed.

5 So it will have a lot more
6 information in one place than the current
7 systems, which are quite disparate in terms of
8 where the reviews are, where the workload
9 assignments are, etcetera.

10 DR. DAI: Yes. Regarding the
11 retrospective data analysis, I have one
12 suggestion. Listening to Min Chen's
13 presentation this morning, apparently that
14 nonserious reports are no longer entered into
15 AERS database if you submit by paper.

16 So I thought within the system you
17 will have some kind of heterogeneous
18 population. Some of those do have long term
19 nonserious reports, some maybe in the same
20 class having only serious reports because they
21 were submitted by paperwork. So you don't
22 enter them anymore, and similarly for private

1 access.

2 Sometime ago, I believe all
3 nonserious reports were entered into AERS a
4 long time ago, and I don't know starting when
5 this stopped. So you know, those kind of data
6 can be compared within the system to see what
7 we gain from continuously reporting and
8 recording nonserious reports.

9 DR. IYASU: Okay. I guess we have
10 had some rich discussion on some areas,
11 especially in terms of focusing the questions
12 that we -- you know, the outcomes or the
13 specific outcome measures that might be of
14 interest to this effort.

15 Are there any additional outcomes
16 that you would like to see? We had a lot of
17 discussion this morning about issues related
18 to communication, and communication meaning to
19 the reporter, and how might we measure that
20 other benefit or to patients, how might we
21 measure that benefit. Anne?

22 DR. TRONTELL: You know, I

1 actually think that the translation into
2 action is a particularly high hurdle to put on
3 the spontaneous reporting system, because we
4 know of many challenges in that communication
5 venue. Again in the future, I think we have
6 hopes that we may have more direct clinical
7 decision support to enable that to happen.

8 So I think that is asking a lot.
9 I find perhaps when you look at metrics like
10 Mara did, the ones that actually are more
11 prescriptive -- You know, a drug withdrawal is
12 very prescriptive. You can't use it any
13 longer. That has an immediate action in the
14 clinical community.

15 Similarly, you know, a new
16 contraindication or a warning as opposed to
17 maybe some of the other labeling changes in
18 the adverse reaction section that are of
19 knowledge but don't necessarily lead to a
20 change in clinical practice. But I actually
21 was going to -- before we go into this
22 particular area, I have one more outcome area

1 which I -- not any way to raise the specter of
2 cost effectiveness, but I think it would be
3 very meaningful to try and actually try and do
4 some cost capture sort of from the business
5 model, from FDA as well as industry.

6 The study done by the CERTS
7 relative to some of the costs of the
8 spontaneous reporting system was really to try
9 and provide some concrete data as to whether
10 or not this relatively inexpensive system, as
11 we've said for so many years, really was.

12 Similarly, sort of if, in fact,
13 some kinds of time studies done on safety
14 evaluators and others to look at sort of
15 percentage of time spent on different reports.
16 Again, if you may ever even be able to presume
17 to develop some criteria for the more valuable
18 reports, how -- You know, as much as you can
19 segment it by the information that's coming in
20 could be very helpful for you even to
21 understand how much of resources are going
22 into this particular effort, and what you

1 might again be able to free up for something
2 that you consider to be more valuable.

3 DR. IYASU: Jim?

4 DR. KOTSANOS: I'd like to add to
5 that, because that's something that goes on in
6 my mind as I look at what we do at our company
7 and what other companies do. That's the
8 relative value of the types of reports and
9 what contribution they make to public health,
10 so when you get solicited reports.

11 When you get reports that are
12 associated with law suits, you know, there's
13 a whole allocation of resources that takes
14 place, and the question becomes how is that
15 information used to address that one category
16 of reports versus focus on another category of
17 reports, the serious reports, the unexpected
18 ones.

19 So that's something, I think, that
20 is testable, evaluable, using a method perhaps
21 outlined by the FDA earlier today or I suppose
22 other approaches, improving quality. What

1 goes through my mind is that would probably be
2 a prospective study.

3 I think it would be useful,
4 especially since we use some of those
5 techniques of targeted surveillance, you
6 know, identified adverse event terms, that we
7 try to get the best information on diagnosis,
8 etcetera. I think something like that would
9 need to be tested prospectively, but I would
10 have to think about it more.

11 DR. DIEK: Gretchen Diek. Again
12 getting back to the studies that we heard
13 about this morning, you still may have some of
14 that information that's available from that.

15 I guess this is a question. Do
16 you have information on whether those were
17 serious or nonserious changes, precautions?
18 I'm assuming they were serious.

19 DR. McADAMS: Is this microphone
20 on? Yes.

21 We have where the label change was
22 made. For the majority of them we have what

1 the labeling change constituted. Was it for
2 liver toxicity, as we mentioned before, things
3 like that.

4 To get back to the source would be
5 another step and being much more involved, and
6 additionally, there is data quality issues the
7 further back in time you go.

8 So is that addressing your
9 question?

10 DR. DIEK: Partially. For
11 instance, right off the top you could -- If
12 some of them were class labels, such as oral
13 contraceptives and, you know, deep vein
14 thrombosis or thoriZen and suicide or even the
15 NSAIDs and the warning that went on NSAIDs
16 recently -- if that's part of the data, if you
17 took that out, how would that change your
18 histogram?

19 DR. McADAMS: Well, this is, I
20 think, where the RFP is really going to be
21 needed, because we were only tracking the most
22 recent change. That class change will be the

1 most recent for some of the drugs in the
2 class, but not necessarily for all of them.

3 So if we step back and we actually
4 look at all safety related labeling changes,
5 that's when you can dig in. That's when you
6 can get to that level. However, the amount of
7 work that would go into that is more than I'm
8 going to be able to do on my own.

9 I think this is something that's
10 going to need a lot of resources, time,
11 manpower. So I think it's completely -- and
12 from my perspective, it is something that is
13 answerable within the context of an RFP. So
14 thank you.

15 DR. KRAMER: So just a question of
16 clarification. Were you envisioning this RFP
17 would go out and whoever -- and that FDA would
18 be funding this research; and would whoever
19 received the RFP become a special government
20 employee to be able to get access to FDA
21 information, or would it have to be someone
22 who would bring their own data and look at it

1 from -- and, say, a sponsored company, for
2 instance? Just what are you envisioning, so
3 we can kind of get a better sense of what you
4 are proposing here?

5 DR. IYASU: Well, Judy can comment
6 on this, too. This is really designed to be
7 done by an outside research outfit, maybe
8 university based or another research group
9 that may have capabilities to answer this
10 enormous effort.

11 Part of what we are asking is what
12 are those capabilities that would be required
13 to undertake such an effort. So I would
14 assume that one of the assumptions that we
15 have is they would have to look at multiple
16 resources in terms of having access to
17 documents and data.

18 In my talk, I talked about
19 confidentiality issues. That may be
20 complicating some of this. So this is -- We
21 haven't resolved that issue completely, but
22 the idea would be that they would have access.

1 I can't say whether this is an FDA effort or
2 not. Do you want to comment on that?

3 DR. STAFFA: No, I agree. In
4 fact, that is something that came up, largely
5 through Mara's work. We realized that we need
6 somebody to be crawling through document rooms
7 and actually having access. But FDA has other
8 contractors that work on site on other things.

9 So it doesn't seem to be something
10 that is insurmountable. The different part of
11 it is that they would probably also have to
12 crawl through industry document rooms as well.

13 So again there may be
14 administrative and technical issues we have to
15 deal with, but that's what we are thinking
16 unless, again, folks on this panel have other
17 ideas of how this could be done. We couldn't
18 figure out another way to do it. And the idea
19 is that, yes, FDA would fund this. Yes --
20 just to be clear.

21 DR. IYASU: Any comments from
22 industry about access?

1 DR. DIEK: I think you could have
2 general -- not necessarily access to
3 documents, but if you had a questionnaire
4 similar to the CERTS questionnaire that was
5 sent out on resource, you could have a
6 general questionnaire that was sent out and
7 maybe targeted for certain industries with
8 respect to the drugs that they had, and say we
9 are interested in the labeling changes that
10 you made in boom-boom-boom for these drugs;
11 can you tell us what the source is.

12 You could have like buckets that
13 people could put in, as opposed to going
14 through, you know, NDA submissions and CBEs
15 and so forth. I think that you could make it
16 a lot simpler if you had a template and some
17 sort of data collection tool that you could
18 give to industry, and they could fill it out
19 and send it back. That's one thing.

20 We also have Booze Allen come in
21 at times and other types of groups that have
22 confidentiality agreements. I wouldn't

1 suggest having open -- here are our files. I
2 mean a lot of our files are archived as well.

3 So I think that, if you could
4 target the information you want, industry
5 could certainly make some of it available, if
6 not everything that you would need to make
7 this sort of assessment.

8 DR. IYASU: Additional comments?

9 DR. PLATT: I'm trying to think
10 how to frame this. Part of this sounds like
11 a case series. We would find certain kinds of
12 outcomes that are interesting, and the
13 question is how did the spontaneous report
14 system contribute to that outcome.

15 So that sounds like it's sort of a
16 historical, anthropological kind of activity,
17 because it would probably need -- because
18 presumably, there was both spontaneous
19 reporting and other kinds of information that
20 contributed to whatever the outcome is, and
21 your investigators will need to have access to
22 the evidence record and probably also the

1 decision makers to try to understand what was
2 going on.

3 So that would have to be a pretty
4 recent set of activities. It would probably
5 be worthwhile also, seems to me, to
6 characterize the base. That is, of the many,
7 many spontaneous reports submitted, it may be
8 worthwhile trying to characterize what the
9 fate of some representative sample was, and
10 representative doesn't have to mean a random
11 sample -- it can be some of these kinds and
12 some of those kinds and some of the other
13 kinds -- to get an idea not only sort of
14 whether there were any successes and what
15 characterized them, but what's the sort of
16 volume of effort that was dedicated to
17 achieving these.

18 That would have to -- clearly,
19 have to be some kind of a fairly small sample
20 from a very large base.

21 DR. IYASU: Judith?

22 DR. KRAMER: Judith Kramer. One

1 question I have always been interested in is
2 once, by whatever mechanism, FDA reviewers
3 determine there is a "signal," I'd be
4 interested even retrospectively in the methods
5 used to try to define denominators and
6 calculate the likely frequency or incidence of
7 this adverse event.

8 That, I presume, could be done
9 retrospectively in terms of what people -- you
10 know, what data sources people used and
11 whether they just went to IMS. I mean, people
12 don't have a sense. Everyone says, well, we
13 don't have a denominator, but somehow we
14 manage to go from signal to concern, and
15 somewhere there's got to be some data in
16 there.

17 DR. IYASU: Well, I think it
18 probably wasn't mentioned specifically in the
19 set of questions that we have, but it's very
20 critical in terms of providing context for the
21 interpretation of any spontaneous adverse
22 events that we get.

1 We do have at the FDA access to
2 IMS, Verispan and Premier, and to the extent
3 that we have patient level information, we try
4 to put the adverse event reports into context
5 by using different tools, reporting rates and
6 the like. But there are obviously a lot of
7 assumptions that go into that.

8 So how we decide whether to use
9 one method, you know, a proportional reporting
10 rate versus another one, is another area that
11 we need to -- The methodologies are not very
12 well standardized, and there isn't really
13 agreement among all researchers about the
14 relative utility of all this in defining the
15 importance of the incidence.

16 You know, they don't provide any
17 incidence data. They just compile the data.
18 So how do you interpret that? It's
19 contextual. So that's another area that
20 probably needs to be addressed also in this
21 effort as part of the scoping for this RFP.

22 I'm wondering if there are other

1 comments from the panel members about this
2 particular area, because I think that it's
3 very critical.

4 DR. EDWARDS: I think there's a
5 huge amount that needs to be done in the area
6 of data mining. Of course, one thing that
7 immediately comes to mind is whether the
8 surrogate denominator that we use in data
9 mining actually would be reflected in the
10 actual drug use data that you could look at.
11 People don't do that. But the whole area of
12 data mining, whether or not, for example, the
13 level of significance we use is the correct
14 one as a threshold to signal is, I think, a
15 very important issue that we are grappling
16 with, and others.

17 So that, I'm sure, is something we
18 ought to put in.

19 DR. IYASU: Yes, Victor? Just
20 state your name.

21 DR. GOGOLAK: Vic Gogolak at
22 DrugLogic.

1 You know, this idea of the signal
2 and where the alert is has been around, and we
3 have been discussing it philosophically and
4 pragmatically. But again, that's of value in
5 looking at what people have done in the past.

6 Right now, we are in the middle of
7 a study for PhRMA, it turns out, looking at
8 some of these algorithms and what they have
9 done. Somebody once asked me, well, if you
10 see a PRR greater than 2, high square to four,
11 is that a true signal, you know? Is that a
12 true positive or is that false positive?

13 I said, from a statistical point
14 of view, if your threshold is PRR greater than
15 2, it's always true. From a statistical point
16 of view, if it's greater than 2, it's greater
17 than 2. It's all in the interpretation.

18 If greater than 2 for the PRR
19 meant that you thought this adverse reaction
20 was due to the drug and 92 percent of the
21 people already had that reaction, your
22 interpretation was wrong.

1 So in a lot of cases, it was the
2 relationship between how people got the signal
3 and what they ultimately determined that's
4 very important, and that is something maybe
5 very hard to do. I mean, I know there have
6 been many studies in the literature looking at
7 -- Almost one by one, they found this
8 reaction.

9 It was clinically validated, and
10 then they went back and they said, oh, this
11 was seen in the literature as a suspected
12 based on some Bayesian, some frequentist and
13 whatever. But that's another massive area in
14 linking the value, because the one word that
15 you use here all the time is value, and I
16 agree with Ralph.

17 I mean, this is value to the
18 patient. We want to make this a safe drug
19 environment for the patients, but that's not
20 operable. You can't operate on that vague
21 statement. You have to say, well, what does
22 it mean. You have to quantify the risk and

1 then communicate to the prescriber what that
2 risk is relative to the benefit of taking the
3 drug.

4 So already we got to pull back
5 into that dirty pragmatic world, and I think
6 only by looking at the history will we get the
7 factors that are important. But if this study
8 is going to also look at the link of data
9 mining -- in other words, how people are going
10 to use this -- then there has to be a look at
11 the relationship between historical decisions
12 and what triggered people to start looking at
13 that.

14 I know that, having spent, you
15 know, 12 or 15 years pre-PRR -- I mean, a lot
16 of the people were doing these things based on
17 pivotal cases long before Steven Evans came up
18 with the criteria at the MCA and so on or the
19 work done at the Uppsala Monitoring Centre or
20 the work done here at the FDA.

21 I think it would be very
22 instructive to the whole community if we had

1 access to that very linkage. So you know, I
2 come back to kind of reiterating what I said
3 before. You need a practical list, but maybe
4 you won't have a complete list.

5 Maybe the first part of the study
6 you do is to say, look, here are examples of
7 the kind of things that are going to be of
8 value. We don't think we have the first list.
9 In fact, you may consider breaking the study
10 into two phases, kind of a diagnostic phase --
11 and that is what do we need to do to know what
12 the proper questions are -- and unfortunately,
13 I spent 40 years in consulting; that's a
14 typical consultant approach -- and then after
15 you define those proper questions, then you
16 could go out and do the interviews. But what
17 will help that first part very much is the
18 kind of indication that we had this morning.

19 There have been decisions. There
20 have been studies. There have been things in
21 the literature. There are -- In each company
22 there are mechanisms that people use for

1 looking at a signal and saying, yes, it's
2 happening enough; we didn't see it in the
3 clinical trials, let's add it to the label.
4 Companies do that voluntarily all the time.

5 That's not very well documented,
6 but it would certainly be instructive, to me,
7 to know whether it was three percent or 30
8 percent or 90 percent of simple label changes
9 were basically spontaneous reports or on some
10 Phase 4 studies. We don't know that.

11 So I think, again, people need to
12 get these simple lists of things and what they
13 can do, and then you could include that as
14 maybe a framework in the RFP that you send
15 out.

16 DR. IYASU: I think that is a good
17 suggestion, and we have compiled a number of
18 ideas that we've gotten from the panel. What
19 we will do is, when we go back, we are going
20 to look at all these ideas and suggestions
21 from the panel, and come up with a prioritized
22 list of how we are going to frame the

1 question.

2 It's been a lot of fruitful, I
3 think, discussion here today. But what I'm
4 hearing is, you know, in terms of research
5 approach, I'm hearing a lot about
6 retrospective versus prospective, and there
7 are some things that we need to look at from
8 a prospective design. There are other things
9 that we need to look at from a retrospective
10 design, and I think that is where we will
11 consider that.

12 The suggestion of maybe phasing
13 the effort into an earlier pilot perhaps to
14 refine the questions -- that's another
15 suggestion that we are getting. Maybe there
16 could be some additional discussion on that.

17 You know, we were talking about
18 time frames earlier in our discussions, and
19 that this effort may take two or three years.
20 But then how does it impact the time that it
21 will take to do a phase 1, a phase 2, or a
22 pilot and then a definitive study.

1 So I'm wondering what other people
2 feel about sort of framing it that way, the
3 pilot versus a definitive sort of expanded
4 study later on, based on the diagnostic of the
5 pilot. I want to hear more discussion on
6 that.

7 We'll take a break soon. I think
8 we've had a long discussion. But if there are
9 comments that anybody wants to make on this
10 issue, please.

11 DR. EDWARDS: On that particular
12 issue, I was actually going to suggest that
13 one thing to take into account, Richard, in my
14 discussion is that we need to, I think, get
15 some metrics for the current situation and
16 then repeat that and see in some years or
17 after sometime, to see if there is any change,
18 and particularly if we are going to change the
19 system.

20 DR. PLATT: This is Richard, and I
21 second the motion. I just want to be sure
22 that we are talking -- I think, in order to do

1 that well -- When we talk about metrics, I
2 think it's going to be very hard to isolate
3 that to the passive surveillance system.

4 So that's part of the concern
5 you've heard me express right along, is that
6 it's this focus on the passive surveillance
7 system that's making me edgy. But I agree
8 completely with how well is the post-marketing
9 safety system doing now, and how well is it
10 doing in the future is critical.

11 DR. IYASU: Any additional
12 comments on this particular issue?

13 I want to ask one additional
14 question, which is sort of in terms of the
15 research approach. We talked about
16 retrospective again and prospective, and I
17 think a lot of it will focus on some
18 quantitative sort of assessment. But how
19 about the issue of quantitative assessments?

20 Is that an approach that should be
21 also entertained as part of this effort?

22 DR. TRONTELL: We had a number of

1 discussions about value, including this one
2 about what metrics we use. I think value
3 decisions are those that are actually very
4 important to consider a variety of stakeholder
5 input. We care probably to hear from
6 patients, health care providers, FDA and
7 industry, of course, advocacy groups.s

8 You know, I don't mean to --
9 pharmacists -- to get some sense of some of
10 the value of this information, even value of
11 reporting, some of this qualitative or semi-
12 qualitative analyses that might allow you to
13 pinpoint some of -- a better sense of societal
14 values and where, in fact, you may have some
15 of the greatest enthusiasm to support the use
16 or change of the system may have merit.

17 I wouldn't spend all your money on
18 that, but I think some preliminary assessment
19 might really help you target.

20 DR. PLATT: I don't see how you
21 can not have historians, really well qualified
22 historians working with you on this

1 retrospective piece, because I think the data
2 -- Usual data methods will fall far short of
3 what you would like to learn.

4 DR. IYASU: Shall we take a break?
5 Okay, we'll take a 10 minute break.

6 (Whereupon, the foregoing matter
7 went off the record at 2:38 p.m. and went back
8 on the record at 3:01 p.m.)

9 DR. IYASU: Okay. We are just
10 about to get started, if you could take your
11 seats, please.

12 I guess we will start with a
13 question that we have been discussing during
14 the break. Rich has to leave soon. So Judy
15 has a question for him that probably would be
16 helpful for us to hear from Rich about his
17 thoughts. So, if you could frame the
18 question, Judy.

19 DR. STAFFA: Sure. Rich, I
20 understand and appreciate your concerns about
21 not focusing too much on what we've been
22 doing, but looking at this evaluation and

1 focusing with an eye to the future of figuring
2 our what kind of passive reporting fits into
3 our future scheme.

4 I'd like to push you a little bit
5 to ask you, if that was on your plate to do,
6 how would you think about doing that? What
7 are the kinds of questions you think require
8 that we really need to answer the most, and
9 then what kind of outcomes would you want to
10 focus on to actually look at those to meet
11 what you see as the need in this arena?

12 DR. PLATT: Well, it seems to me
13 that we, for sure, want to have the ability to
14 identify unanticipated adverse events, because
15 if you say what -- To my mind, the defining
16 success of the passive surveillance system we
17 have is that it has found important things
18 that we had no reason to believe existed, so
19 Fen-Phen or the original association of
20 Guillain-Barre syndrome with immunization.

21 So seems to me that you would want
22 a system that could do that, and it's one of

1 the things that sort of goes beyond
2 statistics. One or two events is enough to
3 change the way you think about things.

4 So I'd say, far and away, that
5 would be the most important. Then sort of a
6 lot of things come downstream from that.

7 I think what else would you care
8 about? It would be things that we are
9 unlikely to find with the other systems that
10 either exist now or we think soon will exist,
11 things that wouldn't appear in an electronic
12 medical record -- Gretchen, we were just
13 talking about that -- either because it
14 doesn't come to medical attention or because,
15 the way we construct medical records, it
16 doesn't appear there.

17 Seems to me, we would need a
18 spontaneous report system for -- more for
19 over-the-counter agents than others, though
20 not completely. So I would stick with that.

21 What else? I'll look to my
22 colleagues. I don't think I'm the most

1 thoughtful in the group about it, but there
2 are a few things that you have to have the
3 capability to do, and no system that we have
4 been discussing is likely to capture them.

5 So I'd say could we then take that
6 as the basis for asking, when the current
7 passive system has worked -- has done those
8 things, what have been the attributes that
9 have let it succeed?

10 When you break apart the whole
11 passive system, are there other elements,
12 particularly ones that are very resource
13 intensive for our society or for the agency in
14 particular, that seem never to have
15 contributed to that kind of outcome. That
16 might give you some handle on understanding
17 where the resource investment has been
18 worthwhile and might continue to be
19 worthwhile.

20 DR. STAFFA: So what I'm hearing
21 you describing is much more of a qualitative
22 analysis as opposed to a quantitative. What

1 we were trying to do with Mara's was we had a
2 great interest in wanting to make this
3 scientifically sound and acceptable and
4 robust, and so there was the element of the
5 overall systematic approach of looking at all
6 drugs, those with and without safety actions,
7 and then doing a survival analysis. But then
8 it was also followed up by that case series
9 where she then drilled down into different
10 arenas and looked at the qualitative issues
11 which, I agree, has to be done as well.

12 What I'm hearing you describe is
13 further on the qualitative side than on the
14 quantitative side.

15 DR. PLATT: Well, I wouldn't make
16 the surveillance system justify itself on the
17 basis of some percentage of successes, because
18 it would be nice to minimize the number of
19 false positives as reports that never go
20 anywhere.

21 So I think that would be an
22 important thing to do, but you only need a

1 couple of successes to justify a pretty
2 substantial enterprise, and I think we need to
3 understand what has contributed to the
4 successes. I think they are much more
5 valuable in their way, because if we
6 understood those well, it might let us
7 understand what has to be preserved by some
8 system or another, and also identify targets
9 at least for streamlining, consolidation,
10 maybe eventually handing off to some other
11 kind of function.

12 DR. DAL PAN: Right.

13 DR. IYASU: Okay, Gretchen?

14 DR. DIEK: I just wanted to add to
15 that. I don't think we should underestimate
16 the importance of having some vehicle for
17 people to report into, in that serves a
18 purpose on its own, that a physician could
19 call someone either at the company or at the
20 FDA and talk to someone, that a patient could
21 call in. I think that that is going to be
22 very hard to measure.

1 DR. IYASU: Additional comments?

2 DR. WOLFE: Well, just taking off
3 on the successes -- I mean, the reason why I
4 mentioned earlier looking backwards at
5 "successes" which are black box warnings and
6 withdrawals -- there's a much smaller number
7 of those than the whole set that Mara looked
8 at this morning -- some very counterintuitive
9 things like Achilles tendon rupture with
10 floroquinalones. No one would dream about
11 anything like that. Unexpected is an
12 understatement about that, and yet that came
13 about through one and two and five and 10
14 adverse reaction reports where no one had
15 jumped off a cliff. There was no athletic
16 contest involved.

17 I think that's a good example of a
18 success. We may dispute as to how soon the
19 success should have occurred, but at least it
20 clearly arose from some spontaneous adverse
21 reaction reports. Obviously, nothing like
22 that showed up in randomized trials. It's not

1 that common.

2 So I think that we can build a
3 number of cases and go back and see how it
4 started, what the data elements were, and
5 still do it in a qualitative kind of way,
6 which is what you are suggesting. That's why
7 the suggestion of a medical historian or a
8 historian is a reasonable one, because that's
9 really -- it's the history of how FDA,
10 whenever it did, arrived at decision making
11 enough to put a black box warning on or take
12 a drug off the market. So I think that's a
13 doable approach, particularly with access to
14 all the documents as a special government
15 employee.

16 DR. IYASU: Thank you for that
17 comment. Are there any additional comments on
18 this line of thought, because I want to move
19 on to another area that we would like some
20 input.

21 That is we had a lot of discussion
22 this morning and also in the afternoon about

1 sort of the need to build on what Mara has
2 done. Of course, the time frame that we
3 looked at in this effort spans from '91 to
4 2006, but in terms of a useful time frame,
5 especially for the retrospective look, what
6 would the panel think would be a useful
7 construct in terms of time frame for the
8 retrospective aspect of looking back at all
9 the questions that we used.

10 Looking at more recent issues, can
11 we go back far enough, even to '91 and sort of
12 drill down the information that we need to get
13 at? What would be a useful time frame?

14 DR. EDWARDS: I approve the logic
15 of what was said this morning. Mara, I think,
16 has it right. The time frame is good. The
17 fact that you can get the data is good. I
18 would go for that and do it.

19 DR. KOTSANOS: I agree. This is
20 Jim Kotsanos. I agree. The time frame is
21 right. I think it's important to be able to
22 track a drug long enough so you can see the

1 changes in the types of information that lead
2 to the changes in whatever defined outcome one
3 has, whether it's safety related actions or
4 some focused one.

5 It would be useful what types of
6 data led to those changes, and I think over
7 time we will find it to change.

8 DR. IYASU: Anne?

9 DR. TRONTELL: I agree for the
10 maximum time frame to sort of get at the issue
11 of whether there might be a time where a
12 certain aged product might have a different
13 input into the spontaneous reporting system,
14 but the AERS system, as I recall, is in its
15 most iteration around 1997.

16 So going back 10 years might be a
17 little bit more -- You know, dealing with the
18 future, you have less paper and a whole
19 different coding system, and then maybe
20 consider even some prospective data collection
21 from the time you start.

22 DR. IYASU: So you are suggesting

1 '97 sort of as a turning point sort of back?

2 DR. TRONTELL: Ninety-seven might
3 have even been a little bit of a transitional
4 year. I would have to defer on whether you
5 would start the clock at '98.

6 DR. STAFFA: Well, then I'm
7 wondering if Mara wouldn't mind commenting, as
8 she crawled through files, as to where she
9 found most of the data actually were there.

10 DR. McADAMS: Yes. I agree 100
11 percent with what Anne said. Our reasonings
12 for choosing the most recent safety related
13 labeling change or marketing withdrawal was
14 that was information that was easy to attain.

15 There were only a few drugs -- I
16 think it was 18 -- in which we had to go
17 through the paper records, go through the
18 document room, find the file folders and
19 search to see what was the most recent.

20 To be looking at all safety
21 related actions is a different -- It's a
22 different question than the most recent. So

1 I think something like '97 would be compatible
2 with both the tracking systems and the AERS
3 system for the most modern view, but still
4 giving us a good length of time.

5 So yes, that seems very reasonable
6 to me. Thank you.

7 DR. IYASU: Anne?

8 DR. TRONTELL: Actually, a
9 question for those from industry, because I
10 think in some -- I hope that industry might
11 have a little more accessible files of just
12 the historical label over time for products.
13 So that you might be able to say more readily
14 than FDA through its paper file systems when
15 the black box warning first appeared on a
16 product. Is that a fair guess?

17 DR. DIEK: Yes.

18 DR. IYASU: Any additional
19 comments on the time frame? I think, you
20 know, what I'm hearing is that '97 may be
21 more doable for a baseline than 2001 -- I mean
22 '91 -- '97-'98. We will have to decide. We

1 are just thinking in terms of a broad brush on
2 the time frame. The specifics, we have to go
3 ahead and sort of decide the turning point.

4 Any additional comments on this?
5 So let me move then to another question that
6 we have and we would like input from the
7 panel.

8 That is regarding some advice
9 about the particular capabilities that an
10 organization from outside FDA needs to have to
11 undertake such a research effort. What would
12 the qualities be that we should be looking for
13 in terms of capabilities and experience
14 background, without naming particular agencies
15 or groups or research organizations. We are
16 looking for the qualities and what we should
17 look for in terms of evaluating them.

18 DR. KOTSANOS: Jim Kotsanos. For
19 starters, I think the group would need to be
20 familiar with the regulatory reports that go
21 in to the agencies, so the PADERS. What
22 comprises a PADER? What is an align list?

1 They need to be familiar with the
2 individual adverse event reports. So they
3 need to be familiar with the data elements.
4 So they need to know the business, and they
5 need to be knowledgeable on what they can
6 find, including correspondences that take
7 place between company and FDA, just, I think,
8 a breadth of information that would start them
9 out on the road to success.

10 DR. DIEK: Maybe Mara could help
11 us, knowing what she had to go through, what
12 sorts of experience do you think would be
13 helpful?

14 DR. IYASU: Going to put her on
15 the spot. Okay? Yes, go ahead.

16 DR. McADAMS: Please feel free,
17 any of the other co-authors, if they would
18 like to jump in at anytime.

19 Our team was actually quite
20 diverse. My background is both in statistics
21 and epidemiology. We had some medical input
22 from both Gerald and Solomon. Judy is a

1 pharmacist and also a PhD epidemiologist.

2 So I was able to get information
3 on reactions for drugs, drug use, thinking
4 about logic, does this make sense from the
5 pharmacy perspective. So we had a very
6 diverse team.

7 Does that answer your question
8 enough? Thank you.

9 DR. DAL PAN: I think Jim makes a
10 good point. Understanding the regulatory
11 process is important, because the information
12 and the process track with each other. So
13 understanding the process of these things is
14 going to be important to knowing where the
15 information is.

16 DR. EDWARDS: What about database
17 quality issues and terminology?

18 DR. IYASU: Can you expand on
19 that?

20 DR. EDWARDS: Always trying to be
21 brief.

22 DR. IYASU: We have time.

1 DR. EDWARDS: Well, anyone who
2 tries to access information from a database
3 ought to understand the problems of getting
4 information into the database, what
5 translations have been made, what terminology
6 has been used, what are the likely
7 misclassifications, groupings. All of that
8 kind of area, I think, is extremely important
9 if you are going to make any sense of the
10 data.

11 DR. IYASU: Yes, Judith.

12 DR. KRAMER: Judith Kramer. I
13 completely agree with the things that Jim
14 listed, but I would also like to add that,
15 since in order -- From all of the discussions
16 we have had, it is clear that we need to
17 access both the data at FDA, and it would be
18 best to also access data at the sponsor
19 companies.

20 So I think it has to be a group
21 that is capable of collaborating with these
22 groups and communicating. For instance, on

1 the project where we did the cost of drug
2 safety, it was a collaborative effort in
3 coming up with the data collection form
4 between the PhRMA members that participated
5 and the researchers at Duke, and there were
6 some researchers who understood the regulatory
7 framework completely and understood safety
8 reporting that fed into the economists doing
9 the development of the questionnaire.

10 So it was a collaborative effort.
11 So having people able to work on both sides,
12 able to work in the FDA world and also able to
13 understand the sponsor data is very important.

14 DR. IYASU: Yes?

15 DR. EDWARDS: Are you going to use
16 global data or just national data?

17 DR. IYASU: Well, I think that is
18 open to question, but my assumption would be
19 that, since sponsors are worldwide, you know,
20 if we are going to access data pertaining to
21 the sponsor files, it would be global.

22 DR. EDWARDS: Well, if so, I think

1 it is an additional requirement to understand
2 how coding and various things are done in the
3 different countries where that data comes
4 from.

5 DR. TRONTELL: Depending on the
6 number of people at FDA or at industry who may
7 be available to assist in this research
8 project, having some individual have some
9 insights into the FDA internal processes and
10 workings would probably be helpful, even as a
11 consultant, to know again some of the stages
12 through which a safety signal is assessed and
13 acted upon with a regulatory change.

14 DR. IYASU: Additional suggestions
15 about capabilities that we should be looking
16 for? How about -- You know, we mentioned
17 areas in terms of cost effectiveness or cost
18 analysis in terms of the net benefit that we
19 would get out of reports.

20 Is that an element -- a group that
21 would have that capability in terms of doing
22 those kind of evaluations, which are sort of

1 different, in a sense. Would that be
2 something that we should be looking for in a
3 prospective offeror?

4 DR. WOLFE: That almost sounds
5 like two different RFPs, though. You know,
6 you have cost estimating skills in one company
7 and not in another. I mean, is that
8 preordained to be part of it doing a
9 cost/benefit analysis as opposed to --

10 DR. IYASU: No. Just part of the
11 spectrum of questions that arose during the
12 discussion, and so in terms of prioritizing
13 which would be the most appropriate, that is
14 something that we would have to go back and
15 sort of discuss later. But I think I just
16 wanted to get some idea about how people feel
17 in that area in terms of do people feel that
18 we need to spend time and effort in looking
19 for capabilities that would weigh on those
20 kind of evaluations.

21 DR. KOTSANOS: Jim Kotsanos. I'm
22 not sure it's needed. I think we are looking

1 at sort of what is the net public health gain
2 by certain types of input data. Clearly,
3 there is going to be a resource cost around
4 different activities that feed into those
5 inputs, but that is a level of analysis I'm
6 not sure that will really help us understand
7 the data that feed into it.

8 So I would probably not go down
9 that path.

10 DR. IYASU: Anne?

11 DR. TRONTELL: Probably as one who
12 in part suggested doing this, and again
13 probably more just for costs, my own
14 experience has been actually working with some
15 health economists who may be accessible, you
16 know, even to get broad parameters to estimate
17 the amount of time spent on different kinds of
18 reports might be helpful.

19 Again, I don't think you need to
20 bring in an econometric consulting firm for
21 this, but I think having the capability -- and
22 again, my own thinking when I proposed that

1 was that you get -- you would actually have to
2 have someone find a way to track how your
3 safety evaluators are spending their time and
4 sort of the gross estimates, things that I
5 think economists are actually pretty good at.

6 DR. IYASU: Okay.

7 DR. DAI: Yes. the kind of cost
8 I'm thinking about is not really dollar per
9 se, but more like, say, for example, you have
10 to follow up a report, a million nonserious
11 reports in order to find one to make label
12 changes. That kind of thing is -- Maybe you
13 can call it cost/benefit. I don't know.
14 It's not money per se, but I think it should
15 be in the equation.

16 In terms of the team to work, the
17 more I'm thinking about, you know, based on my
18 life experience, it seems more important to
19 have a team rather than individual person,
20 because you do need to know the regulatory
21 reporting requirements.

22 I can imagine for a researcher in

1 academia who, for example -- not just academic
2 but any other setting -- you will not
3 understand really what are for the domestic
4 reports, only serious reported, and nonserious
5 may or may not be entered, and foreign only
6 serious and labeled reports entered.

7 So the interpretation has to be
8 around this environment. So I'm thinking
9 about more like a team, somebody probably good
10 with the methodology, somebody good with the
11 regulations, somebody with, say, costs, you
12 know, in that parameter.

13 So it's a team. Even Judy's idea
14 was -- I think it was good, like the CERTS
15 work with industry. But maybe even, say,
16 PhRMA may be responding to RFP, but with
17 other, say, people from CERT, from Duke or
18 something.

19 So I think a team more important.

20 DR. KRAMER: Judith Kramer. Cost
21 effectiveness: I think we should be clear
22 which group we are talking about assessing

1 costs and be clear about what has already been
2 done.

3 So similar in the way that the
4 Tufts Center estimated the cost of drug
5 development and then did an update a number of
6 years later, we already have had a lot of
7 investment in coming up with a survey to
8 assess the overall cost of drug safety within
9 the PhRMA companies, and that could be
10 repeated.

11 Now that wasn't segmented into
12 just spontaneous reporting. That could be
13 done fairly easily by some additional
14 questions, but that -- I would say, rather
15 than reinventing the wheel, if you really want
16 to know an update on costs, you should go back
17 to the same people and have them update it or
18 at least use the same instrument, if not have
19 the same people interpret it.

20 What Anne raised that, I don't
21 think, has been done is the resource
22 investment within the agency. The only thing

1 we did in that manuscript on the cost of drug
2 safety for the FDA was to quote the budget for
3 the same year that we estimated the resource
4 expenditure within the company.

5 So it would be new information and
6 interesting, but I'm not sure myself how
7 critical it is. I think the one huge missing
8 piece is the benefit side. You know, what are
9 we getting out of this system, and I think
10 that's why we are here today.

11 DR. IYASU: Okay.

12 DR. GOGOLAK: Vic Gogolak,
13 DrugLogic.

14 Now I would tend to agree that
15 cost at some point might be important, but the
16 elements that are here do seem quite separate,
17 and my concern in a lot of these studies is
18 they get very complicated very quickly. This,
19 just from the discussion this morning and this
20 afternoon, seems quite difficult enough for
21 any one effort we have already -- well, maybe
22 I broached the idea of a phase, simply because

1 I'm listening to all these factors.

2 Organizing them will be terrible,
3 and I just think to keep it as clean as
4 possible. If there is an interesting in the
5 agency to know what resource benefits are, you
6 could probably carve that out and get a small
7 study done very pointed, and other issues
8 might come up. But I think this broad
9 relationship between the activity, the value
10 and the specific metrics that you want to
11 accumulate has to be communicated to the
12 bidders very clearly, and I think it is an
13 excellent idea that you put right up front
14 what these criteria are.

15 We don't want just people out of
16 central casting. We want people that have
17 domain expertise. We don't want them
18 learning. After 40 years of consulting, we
19 don't want OJT for consultants. I'm sorry.
20 I think you need to get people who have a
21 sensitivity but are independent.

22 I think the other important

1 criteria, besides being somewhat objective and
2 independent of all other pieces, they have to
3 be able to deal with the practicalities of
4 confidentiality.

5 They can't be tied to anything
6 where there would be any suspicion that seeing
7 this data would be bad, because they will just
8 -- the study would get cut off.

9 So I think there are going to be
10 some very important criteria, like
11 confidentiality, objective and so on, that's
12 going to narrow it into a group of people, and
13 then by the time you put on domain expertise
14 you don't want to put too many other things on
15 top of that. Just keep it manageable.

16 DR. IYASU: Right. Thank you.
17 Are there any -- We have one there before we
18 go to the open public hearing. Any additional
19 final comments from anybody? Okay.

20 So we are going to go to the open
21 public hearing section of the discussion, and
22 I think we have one registered speaker, Rick

1 Kingston.

2 There is a switch on the bottom of
3 that, if you could use that one.

4 DR. KINGSTON: Is this all right?

5 DR. IYASU: Yes.

6 DR. KINGSTON: Okay. First, I
7 would very much like to thank the panel for
8 letting me make these comments this afternoon.

9 My name is Rick Kingston, and I'm
10 the President of Regulatory and Scientific
11 Affairs for the SafetyCall International
12 Poison Center in the twin cities of
13 Minneapolis and St. Paul, and I am also a
14 clinical professor of pharmacy at the
15 University of Minnesota, and previously I was
16 the Director of the Minnesota Regional Poison
17 Center, which is one of the largest poison
18 centers in the country, serving a five-state
19 area.

20 So I've got about 28 years
21 experience in managing and documenting,
22 tabulating adverse events. In my current

1 practice, we continue to do that type of
2 activity. We handle well in excess of 100,000
3 units -- or adverse event incidents per year,
4 and we are little bit unique in that we also
5 handle animal related events as well.

6 So we have a full veterinary staff
7 that respond to spontaneous events involving
8 animals, as well as physicians and pharmacists
9 that respond to events involving humans, and
10 we do this for corporate clients.

11 Then essentially over my career I
12 have probably handled in excess of 50,000
13 adverse events myself. So I have some
14 experience on the front lines in terms of the
15 types of data that gets collected, how it gets
16 collected and ultimately ends up in the hands
17 of FDA or EPA or other regulators.

18 I have really been struck by a
19 number of things as I have listened to the
20 different comments today and taken a look at
21 the whole area of spontaneous adverse events.
22 A couple of things I wanted to point out.

1 When you are thinking about
2 designing RFPs or asking for input from the
3 outside, some of the questions that have been
4 raised, and maybe some of the comments that I
5 have will fall into things that were mentioned
6 this morning -- But first of all, what role
7 does properly designed data collection versus
8 tabulation tools make in the report integrity?

9 One thing that I've found over the
10 years is that, when you are on the front lines
11 handling spontaneously reported data, the type
12 of tool that you use makes an incredible
13 difference, and I can guaranty you, the tool
14 that we use doesn't look anything like a 3500-
15 A.

16 So you need to have tools that
17 allow people to collect information, the way
18 that it flows in these spontaneous types of
19 reports so you get good quality information,
20 but you catch that on the fly.

21 Another thing that I found
22 striking as I was listening to the comments

1 all day today is, you know, when you really
2 think about this, this is really all about the
3 patient. But I haven't heard one person
4 comment about the role of the patient in this
5 process, in either educating the public about
6 the need to report spontaneous reported events
7 if they suspect something is going on, whether
8 they report it to their physician or to a
9 company whose product that they have just
10 purchased. They've used it; they experience
11 some unexpected type of event, and they want
12 to know if there is some type of relationship.

13 It is really talking about
14 maximally engaging the patient in that process
15 so that they can be prepared to share
16 meaningful information and, once they make
17 contact with somebody either in a regulatory
18 agency or maybe in a clinical practice, within
19 a company's adverse event center, their
20 product safety group, how they can continue to
21 provide information on an ongoing basis
22 potentially. I think that there are some

1 unique possibilities there.

2 That kind of moves into the next
3 area, the aspect of strike while the iron is
4 hot. What I mean by that is, you know, when
5 we respond and get information from consumers
6 when they have some type of an adverse event,
7 one of the biggest challenges is getting as
8 much information as you can while the patient
9 and their health care practitioner are
10 maximally engaged.

11 By the time this ultimately gets
12 to the FDA, you know, six months later and
13 somebody gets around to looking at it, you try
14 to get hold of that patient, even track them
15 down. I mean, you can't find that
16 information. You really need to focus on
17 being able to maximally engage patients and
18 their health care practitioners when the time
19 is there, when they need information. That
20 needs to flow in a couple of different
21 directions. That's really kind of another
22 aspect as well.

1 Another thing is how can you
2 better screen adverse events relationships?
3 You know, people always talk about spontaneous
4 reported data and looking at cause and effect
5 relationships, and you don't establish cause
6 and effect relationships with this kind of
7 data. You look for associations.

8 There may be better ways to screen
9 all the events that come in and put the
10 emphasis on the ones that rise to a certain
11 level, and that is certainly one thing that we
12 do in our center. We have a process that we
13 go through to put emphasis on the types of
14 cases that really require that kind of input.

15 That kind of flows into the next
16 thing of categorization of data versus
17 tabulation of data. If you look at a 3500-A,
18 it is basically fill in the blanks and, you
19 know, a monkey can do that.

20 You go through each one of the
21 steps, and you can ask a question. You fill
22 it out. But where does it ask about frontline

1 clinicians giving clinical impressions versus
2 simply filling in those blanks?

3 I think that you have to realize,
4 it's those people on the front lines that are
5 collecting information that ultimately you are
6 going to use two steps or three steps removed
7 from that data collection process.

8 The other thing is about do
9 interviewing skills matter? One of the things
10 that I notice even among my own staff, some of
11 the junior staff -- you know, they will come
12 to me with a case that they are currently
13 handling. They give me the information. Then
14 when I talk to the patient or the doc, it's a
15 whole different story. I get a whole lot more
16 information.

17 Obviously, some experience takes
18 place there, but that really gets into the
19 idea of what is the benefit of training a
20 frontline staff in responding to and managing
21 and report of these adverse events.

22 You know, a lot of times it's your

1 clinical pharmacist, as a number of folks had
2 mentioned earlier, that are on the front lines
3 doing this. But what organized training
4 programs do we have to train practitioners
5 that are on the front lines. That is their
6 front line responsibility to collect this kind
7 of data. I haven't seen a lot of this come
8 through over the years.

9 So we kind of come full circle.
10 You take a look at what your potential goals
11 are, and you have to look at that in the
12 bigger picture. I've heard people talk about
13 the pros and cons of -- you know, when do you
14 stop collecting adverse event data?

15 I think, again, you have to get
16 back to the patient goals. First of all, is
17 there inherent toxicity? Is there something
18 that happens predictably with a certain
19 percentage of the patients with that
20 particular drug we just didn't pick up in our
21 clinical trials, because our population it is
22 marketed to is obviously larger than the

1 population that we studied?

2 Secondly, are there interactions
3 with new drugs that have come on the market?
4 A lot of that old drug is still being used.
5 Are there other products, such as natural
6 products, herbal remedies, dietary
7 supplements, and with the new adverse event
8 reporting systems with dietary supplements and
9 OTC drugs, I think it's got huge impact on
10 what's going to happen in that particular
11 area.

12 Then maybe another aspect is new
13 uses. You know, off-label uses is one
14 practitioner finds a new use. It ends up
15 getting promoted to their colleagues. You
16 know, physicians have the right and the
17 authority to prescribe a drug for whatever
18 indication that they think that it would best
19 serve that individual patient.

20 So there's going to be new uses of
21 products, and there's also going to be new
22 trends in terms of what patients decide to do

1 with that drug or that OTC drug or with that
2 dietary supplement or what have you that's
3 outside of what the labeling states. So being
4 able to monitor that.

5 Then lastly, I think we have to
6 talk about consumer confidence, and that's
7 where I talk about product integrity and
8 looking at when we talked about whether or not
9 we need to do ongoing surveillance for
10 spontaneous reports.

11 I always look at this in the
12 context of contamination or, you know, it
13 could be potentially JMP types of issues.
14 Certainly, with dietary supplements that is
15 going to be a big issue.

16 I just did a study with the
17 University of Kansas -- University of Missouri
18 group, and they were taking a look at dietary
19 supplements and herbals and looking at the
20 adverse events and looking at cause and effect
21 relationships, and what was amazing was
22 looking at hundreds of these. No analysis of

1 any of the ingredients that were supposedly
2 associated with some type of an adverse event.
3 These were looking at published reports.

4 So I think incorporating some type
5 of an analysis process, especially as it
6 relates to natural products in that capacity.

7 Then the other thing has to do
8 with the Homeland Security aspect and consumer
9 confidence.

10 Our Poison Center -- When I was
11 the Director of the Minnesota Poison Center,
12 I was the first Director. We opened it on
13 September 30, 1982, two hours before an
14 incident involving Tylenol and cyanide. So,
15 you know, people still give me grief about
16 that. You know, we had like 2000 calls in the
17 first 24 hours. That's how we launched our
18 center.

19 It kind of gets back to the idea
20 that, if there is something that happens like
21 that -- and it doesn't matter if it's a
22 mainstream pharmaceutical, the dietary

1 supplement, some type of consumer product --
2 are there systems or processes in place, other
3 than just serendipitous discovery, that is
4 going to identify that?

5 That's why you have to have this
6 ongoing system of surveillance, to keep that
7 in mind.

8 The last thing that I might
9 mention really relates to the impact of FDA in
10 determining and communicating best practices.
11 As all of you know, with the new adverse event
12 reporting requirements for dietary supplements
13 and OTC drugs, FDA issued two guidance
14 documents, one for the drug side and one of
15 the dietary supplement.

16 One of the things I was encouraged
17 to see is that they did recommend, strongly
18 encouraged the use of health care
19 practitioners and health care professionals
20 who are skilled in this type of area to
21 collect these types of incidents.

22 What I found interesting is that

1 many of the same organizations that were very
2 pro in seeing this guidance essentially put --
3 or see the adverse event reporting requirement
4 go into law are absolutely opposed to having
5 health care practitioners actually collect the
6 adverse data that is coming into these
7 companies, which seems to be strange to me,
8 for some reason.

9 I know that Dr. Wolfe can
10 certainly attest to what the experience was
11 with Ephedra. It wasn't that MetabolLife
12 didn't have people trying to communicate that
13 there was a problem. It's that they had all
14 these inquiries coming in, and even had health
15 care practitioners that were supposedly
16 fielding this.

17 Apparently, they didn't have any
18 training or they didn't have any documentation
19 of practices, best practices, and how to
20 collect that information and share it
21 ultimately.

22 So I think it is going to very,

1 very important that the FDA stand their ground
2 and make sure that they communicate best
3 practices and give some guidance.

4 I think one of the gentlemen
5 earlier today from one of the drug companies
6 mentioned you tell us what you want, and we
7 will make that happen. They need to get
8 guidance and consideration for what really
9 constitutes best practices and the types of
10 tools that can best be used to accomplish
11 that.

12 So thanks very much.

13 DR. IYASU: Thank you very much.

14 I would like now to open the rest
15 of the discussion to actually the panel
16 members who were part of the discussion this
17 morning, and I know that several of you have
18 expressed an interest to comment on the
19 session in the afternoon.

20 DR. STANG: Paul Stang, J&J.

21 I want to go back to a string of
22 thoughts we had earlier, which had to do with

1 measuring the value of spontaneous data, and
2 we kind of vacillated between the value of the
3 data versus the value of the system that
4 collects the data.

5 It occurred to me that -- and I
6 want to pick up a little bit about
7 transparency in decision making and how that
8 data are used.

9 So if you look at the type of
10 data, the different data types, and we've
11 discussed quite a bit about the different data
12 types that might go into a decision,
13 regardless of how you define what that
14 decision is, a black box, a withdrawal, a
15 label change, it seems to me that one thing
16 you might want to consider as a research
17 project is setting up a simulation and
18 actually simulating and varying the
19 information that is given or the type of
20 information that is given, and what decision
21 is actually arrived at by any number of people
22 using that type of information.

1 The advantage of doing a
2 simulation like that is you have total control
3 over the quality, the type of information, the
4 fact that it is repeatable across any number
5 of people. And I would encourage you to
6 include in that group not only safety
7 experienced people, either at the agency or in
8 industry or in academia, but also go out into
9 the general medical and clinical population;
10 because what you may find with those
11 simulations is they give a different weight of
12 evidence or a different strength to different
13 types of information.

14 When I started thinking about
15 this, it also occurred to me that once you
16 start understanding how strongly people view
17 certain types of data -- so it may be -- I
18 think someone brought up animal tox data
19 almost should trump a lot of other different
20 types of data. But once you start seeing the
21 interplay here, it might also help you with
22 the labeling at the end of the day, because it

1 may be that you learn some consistency that
2 what people really need to know about are
3 these particular types of information, more so
4 than others, to arrive at or give insight into
5 some of their clinical decision making.

6 It also may give you some insight
7 into what continuing education or CME
8 offerings need to be offered or thought of as
9 part o the larger effort.

10 I think we brought up the idea of
11 CME before, but it just occurred to me that
12 using simulation is a way of building a
13 rational data collection method to understand
14 and get at some of the issues that were
15 brought up a bit earlier in the afternoon
16 about how do we make these decisions, what
17 pieces of information feed into them, and how
18 do we balance some of those.

19 I realize it's not perfect, but I
20 also see everybody struggling with historical
21 versus prospective, and this kind of takes
22 that out of the mix, I think, and makes it

1 independent almost of the current system.

2 So it's just a thought. It may be
3 also to -- I guess Rich has left, but one
4 other piece of that information is information
5 that is coming from the electronic health
6 record systems, for those in it.

7 So this might give you insight as
8 to what that role might be over time, as those
9 systems become more and more plentiful and
10 more and more accessible.

11 So it's just a thought, because it
12 is a separate research endeavor, and it has
13 resource implications.

14 DR. IYASU: Thank you, Paul. Are
15 there any other members from this morning's
16 panel who would like to comment? Judith?

17 DR. JONES: Judith Jones.

18 I'd like to make two or three
19 comments that follow on my original question
20 this morning about Mara's research, and I
21 don't think it's been brought up per se. But
22 one question would be to look at the outcomes

1 of her research from a sort of epidemiologic
2 perspective.

3 I personally probably have an
4 institutional memory of about 50 percent of
5 most things that have happened since 1980,
6 most withdrawals, and they are complex, and
7 actually there is a book that is coming out
8 shortly by Hartzema and Tilson that has a lot
9 of detailed histories of some of the major
10 things that would be a good resource as you
11 are thinking about this.

12 A high proportion, I think, of
13 this -- and this would be something that -- I
14 mean, my hypothesis is a high proportion of
15 these events, whether they are black box,
16 warnings, precautions or withdrawals, really
17 relate to events that are quite rare, and it
18 really goes back to what Victor was pointing
19 out, that in fact, there are circumstances
20 where there is not one risk factor but there
21 may be two or three risk factors, often drug
22 interactions.

1 The probability of this happening
2 in any defined cohort of even 50 million
3 people is not high. In other words, we are
4 dealing with genetic predispositions,
5 interactions, and actually misuse of drugs by
6 physician, whether it is by dose or other
7 situations. Those are only captured by this
8 system.

9 In fact, you can take a look at
10 the data you have looked at and prove me
11 wrong. I think there may be some common
12 situations, but many of them are very rare
13 circumstances, which is probably, to me, the
14 strongest argument for maintaining a passive
15 system.

16 Certainly, birth defects is an
17 obvious example, because most of them are so
18 rare unless we've got the very common ones.

19 So I think a careful look at just
20 the frequency of the events that are covered
21 or stimulate a regulatory change would be
22 very, very helpful, because I think they are

1 less than one in 10,000 often, and I'll make
2 a comment about the active versus passive.

3 The second possible thing that
4 could be put in the RFP really is to link
5 those events to actually changes in population
6 health, if you will, or pharmacist action,
7 physician action or even outcomes.

8 Now we did a study that actually
9 FDA cited for a while. It actually took
10 Cisipride, looked at patients who were taking
11 Cisipride and one of the warned-about
12 interactions to find out both whether people
13 paid attention to it and where the locus of
14 control was. And in fact, it was mostly at
15 the pharmacy.

16 In other words, 95 percent of the
17 interacting prescriptions were ignored at the
18 pharmacy. Fifty percent of them were by the
19 physician, and it's published in JAMA two or
20 three years ago.

21 I think linking each of these to
22 any sort of health outcome, which is really

1 what we are about, would be very valuable, and
2 we've got many of the epidemiologic systems
3 where you could take a sample of those and
4 say, well, even if we warned, even if we had
5 a good outcome, did we make any impact on the
6 public health, because that is really what it
7 is all about. That may help you value the
8 system at some point.

9 The other follow-on from that
10 really relates to Paul's suggestion of a
11 simulation. I love simulations. I think this
12 would be a particularly hard one, but what you
13 really want to do is to find the right
14 limiting step in these decisions, if there is
15 a common one.

16 If we could do that, that would be
17 a way to refine the system. I agree that
18 there is a tremendous amount of effort and
19 time and paper and shuffling and electronic
20 shuffling that never comes to anything. But
21 in fact, the jewels that come out of it still
22 make it worth doing, and maybe there are

1 efficiencies in there.

2 The final issue is -- and I think
3 most people don't really think it is an active
4 system versus a passive system. I've made an
5 argument for the value of a passive system,
6 and I hope we never do away with that.

7 The active surveillance -- If you
8 do power calculations, it is really hard to
9 imagine that you are going to detect those
10 rare events.

11 The second thing is that many
12 active systems really have the Hawthorne
13 effect. For example, the electronic medical
14 record, to the extent that they control
15 decision making by physicians, you are going
16 to really change the decisions and the use of
17 drugs by those physicians compared with those
18 physicians who are not using electronic
19 systems, which are sort of in a free, non-
20 decision making mode.

21 I think until we get consistent
22 electronic medical records, you are always

1 going to have different prompt systems and
2 others.

3 In our study of Cisipride, we
4 found that people probably turned off the
5 prompts when they dispense interacting drugs.
6 So there's all kinds of human behavior factors
7 that you may have to think about in the active
8 surveillance system.

9 So they may be useful -- Final
10 point. They may be useful for certain things,
11 and that would be rather common events that
12 are not well covered and not quantified.
13 Public health-wise, Warfarin adverse reactions
14 are the most common problem. They are not
15 reported. They are not dealt with in any
16 effective way.

17 An active surveillance system
18 could actually get at the risk factors for
19 those and perhaps eliminate that public health
20 problem, which is not necessarily the purview
21 of FDA. Maybe it's the hospital's; maybe it's
22 the system's. But it is one that we just keep

1 overlooking, and every year we hear, you know,
2 when you look at all the adverse effects, they
3 are very common things like Warfarin
4 reactions.

5 So -- but an FDA surveillance
6 system on a new drug can actually get at that
7 rather efficiently, because you don't need a
8 lot of power, because it is more common and it
9 may capture the symptomatic things that are
10 never captured in claims systems and may not
11 be captured in efficient electronic medical
12 records systems. Thank you.

13 DR. IYASU: Any other comments from
14 the other panel members from this morning?
15 Okay. Bob?

16 DR. SHARRAR: Bob Sharrar, Merck.
17 I just have two additional comments to make.

18 We've talked about the time that
19 the drug is put on the market before the
20 signal is detected. I think that is one
21 variable. But I think we have to keep in
22 mind, it's really exposure.

1 In other words, if you are looking
2 at a rare event that may only occur in 100,000
3 people, you are not going to detect the signal
4 until 100,000 people have taken it. So you
5 really have to keep in mind what is the
6 population exposure before the signal is
7 detected. So that's the real criteria, not
8 necessarily the time in the market.

9 The second point I want to make
10 is, you know, as everybody knows, I'm a real
11 fan of post-marketing surveillance. I believe
12 in it very strongly.

13 I think we need to have better
14 methodology developed to how can we use the
15 data that we have. Now we do use the data now
16 for evaluating individual cases. We use the
17 data now for putting together case series
18 where we can kind of get an epidemiologic
19 description of the clinical characteristics.
20 But we have never used, at least to my
21 knowledge, the database to try to come up with
22 maybe a case control study.

1 Now we have in our database, for
2 an example, a number of individuals that have
3 taken a particular drug, and I'll use a drug
4 like statins. Some of the people on statins
5 developed rhabdomyolysis. Other people on
6 statins did not.

7 Can we use the database to pull
8 out those people that got rhabdomyolysis, pull
9 out a control group of other people in the
10 database on a statin that did not develop
11 rhabdomyolysis, and can we do a case control
12 study to see if we can identify a factor that
13 might explain why some people on the product
14 got rhabdomyolysis and other on the product
15 did not?

16 It is kind of a data mining, in a
17 sense, but it's not a disproportionality
18 analysis. It is trying to -- What is the data
19 trying to tell us? I'd like to see more of
20 that being done.

21 One final point about post-
22 marketing surveillance. You know, product

1 safety is really a public health issue, and
2 when you think about post-marketing
3 surveillance or passive surveillance, that's
4 really the voice of the public telling you
5 what the problems are.

6 DR. IYASU: Yes. Okay. Well, it
7 seems like we don't have anymore comments from
8 this morning's panel. So I will open it up
9 for public comment, and if there is anybody
10 from the -- Okay, Judy -- Rosalyn, okay.

11 If you can identify yourself, and
12 use the mic.

13 DR. BRIGHT: My name is Rosalyn
14 Bright. I'm an epidemiologist with FDA, and
15 I have a few ideas about study design, and
16 I've been thinking about the process where an
17 adverse event report comes into FDA and then
18 there are lots of different things that can
19 happen to it, kind of, and you can build
20 something kind of like a decision tree,
21 because basically there are decisions made
22 about the adverse event report as it gets

1 looked at, and someone thinks they are
2 concerned about it or not.

3 I think it would be good to try to
4 build into the design what happens -- what it
5 is about the adverse event reports that don't
6 ever make it to being called a signal or, once
7 they are called a signal, don't ever make it
8 to some kind of regulatory action; because I
9 think the comparison between those kinds of
10 reports and the ones that do make it to action
11 or some other intermediate step that's in the
12 study is going to be valuable to figuring out
13 what is it about adverse event reports that
14 are useful, what factors are useful, and which
15 factors are not -- or what features, I should
16 say, more than factors.

17 It also might be useful in that
18 exercise to also divide up the kinds of
19 signals and adverse event reports we have by
20 whether it seems like those would be better
21 picked up in an active surveillance system or
22 not, because that can help you target where

1 you are going to put the emphasis, if you want
2 to further develop passive surveillance as a
3 complement to active surveillance.

4 So those are my main two comments.

5 DR. IYASU: Thank you very much.

6 Yes? Can you state your name, and use the
7 mic, please?

8 DR. POLLARA: Is it on now?

9 My name is Victor Pollara. I'm
10 from Noblis. My area of expertise is
11 computation in biology and natural language
12 processing.

13 I wanted to address the -- We talk
14 about signals. I just wanted to present my
15 thoughts about signals, is that, for example,
16 Richard Platt was -- We discussed active; we
17 discussed passive, and a signal is the yin of
18 the yang of the background.

19 So every dataset you have has a
20 natural background and, therefore there may
21 not be a signal that you would detect from
22 that.

1 So when we talk about
2 understanding what is a signal and how to
3 define a signal, it is entirely dependent on
4 the dataset that you are looking at. So in an
5 active dataset from an HMO or something like
6 that, there is specific kind of data that are
7 there.

8 Whether you are looking at fixed
9 fields, codes or mining the natural language
10 with the information extraction, you are going
11 to be able to get certain things out of that
12 dataset, and what you can get out of that by
13 your computational techniques determines what
14 really could be a signal from that.

15 So there's certain things you will
16 get, and I think Rosalyn mentioned this, is
17 there's certain things you will get out of an
18 active dataset, and Judith mentioned this,
19 which was about the common things that have
20 mild effects. They are adverse events, but
21 they are not -- they don't rise to the level
22 of the spontaneous reporting system.

1 So in an active system, you have a
2 specific kind of data. And when you look for
3 a signal there, the definition of a signal is
4 going to be dependent on that kind of data.

5 In the AERS, for example, it's an
6 entirely different dataset, kind of data, and
7 it tends toward more rare events and more
8 severe events. So what is a signal in that
9 dataset will be different.

10 So my suggestion for an RFP would
11 be to seriously scientifically study the kinds
12 of datasets we have available, and try to
13 understand how we would, not in one stroke,
14 but in an iterative way understand what we
15 mean by a signal and how to define a signal.
16 So scientifically, iteratively arrive at what
17 we consider a signal in an active set and in
18 the AERS.

19 By doing so, we will understand
20 where the active system has its strengths and
21 where the spontaneous system has its
22 strengths, and where the signals would be

1 detected better in one or the other.

2 The other thought I had is about
3 that what happens when someone who is running
4 an active system comes up with a signal? What
5 do they do with it? They send it here, don't
6 they?

7 So they spontaneously would report
8 it here anyway. So the AERS is not going to
9 go away, by any means. But the point is,
10 where you could detect a signal, how soon you
11 could detect a signal, and by methods that are
12 suited to that particular dataset.

13 So my suggestion for an RFP would
14 be to seriously think about understanding the
15 different kinds of data and understanding --
16 trying to understand what we mean by a signal
17 in these various kinds of data, and trying to
18 do that in a scientific way. Thanks.

19 DR. IYASU: Right. Thank you.

20 Are there any additional comments
21 from the public?

22 DR. LAUDON: Mark Laudon from

1 Aries Global again.

2 The question of whether this was
3 going to be an international study was raised
4 briefly earlier. Of course, that poses the
5 question, which maybe will be part of the
6 study, which is whether spontaneous reporting
7 is yielding signals faster in one environment
8 than the other.

9 Of course, that's going to need
10 you to go look at data in Europe as well,
11 because if they are detecting signals faster
12 than you based on the same spontaneous cases,
13 then that's an interesting challenge.

14 DR. IYASU: Great. Are there any
15 additional comments from the public?

16 DR. STAFFA: I want to thank
17 everybody for all of your thoughtful input.

18 I actually had a mind to try to
19 summarize what I have learned today, but I
20 think it might actually start another
21 discussion, and I think we are all pretty
22 beat.

1 So suffice to say, I learned a
2 lot. I got a lot of ideas. I think
3 benefiting from the total experience of all
4 the folks here who have been thinking about
5 these kinds of systems and how to improve them
6 from many more years than I have has really
7 been helpful.

8 I'll ask Solomon if he wants to
9 add. But I also want to encourage folks, if
10 something occurs to you on your way home or
11 later, we do have a docket open, and we would
12 encourage people to submit anything they would
13 like to the docket.

14 Fran wants to make a final
15 comment. So go, Fran.

16 DR. CUNNINGHAM: I'm going to
17 comment, I guess, on key question number 6,
18 which is what do we know about non-reported --

19 DR. STAFFA: And I didn't want to
20 start another discussion?

21 DR. CUNNINGHAM: I just have to
22 say something.

1 What do we know about non-reported
2 AEs or characteristics associated with non-
3 reporting?

4 I think the answer lies with
5 everything that's been stated here about the
6 different types of databases and ways to look
7 at non-reported events.

8 One of the potential ways to do it
9 is to take different methods of reporting
10 systems -- take a spontaneous reporting
11 system, take a physician reported system, take
12 an integrated database reporting system, cross
13 along the three or look at the three, and see
14 which one manifests what hasn't been reported.

15 That may occur differently based
16 on the event that you are looking for. So I
17 think that is something to think about.

18 DR. BRIGHT: That's been done.

19 DR. CUNNINGHAM: Perfect.

20 DR. IYASU: Well, thank you very
21 much. I, too, want to extend my thanks. I
22 think we learned quite a lot today, and we

1 have a lot of work to do in terms of digesting
2 all this information and trying to frame it
3 into some kind of RFP. And I really thank
4 you. Gerald, do you want to say a few words?

5 DR. DAL PAN: I, too, would like
6 to thank our panel here, the morning panel and
7 the afternoon panel and all the FDA staff who
8 worked so hard to make this such a successful
9 meeting. Thank you.

10 DR. IYASU: And Lana?

11 DR. PAULS: The only thing I
12 wanted to say is that many people have asked
13 me about the slides that were presented by the
14 FDA today. I will do my best to get them to
15 the dockets people tomorrow. So you should be
16 able to view them very soon.

17 Just to reiterate Judy's point,
18 the docket is open until February 29th, and we
19 invite all public and industry comments on
20 that. Thank you very much.

21 (Whereupon, the foregoing matter
22 went off the record at 4:01 p.m.)

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