

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

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FOOD AND DRUG ADMINISTRATION (FDA)

STUDY APPROACHES AND METHODS TO EVALUATE
THE SAFETY OF DRUGS AND BIOLOGICAL PRODUCTS
DURING PREGNANCY IN THE POST-APPROVAL SETTING

PUBLIC MEETING
Docket Number FDA-2014-N-0157

Volume I
Wednesday, May 28, 2014
8:07 a.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31, Conference Center
The Great Room, Room 1503
Silver Spring, Maryland

Reported by: Erick McNair
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2

1 A P P E A R A N C E S

2 Panelists:

3 JESSICA ALBANO, PhD, MPH

4 SUSAN E. ANDRADE, ScD

5 ELISE BERLINER, PhD

6 CHRISTINA CHAMBERS, PhD, MPH

7 AVA MARIE S. CONLIN, DO, MPH*

8 COL TRINKA COSTER

9 JANET CRAGAN, MD, MPH

10 MICHAEL F. GREENE, MD

11 CRAIG HANSEN, PhD

12 SONIA HERNANDEZ-DIAZ, MD, DrPH

13 LEWIS B. HOLMES, MD

14 MARGARET (PEGGY) HONEIN, PhD, MPH*

15 DIANA L. JOHNSON, MS

16 ALLEN A. MITCHELL, MD

17

18 Industry Representatives:

19 ADEL ABOU-ALI, PharmD, ScD, MS

20 ADRIAN DANA, MD

21

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Food and Drug Administration Public Meeting 05-28-2014

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A P P E A R A N C E S (Cont.)

3 FDA Representatives:

4

HODA T. HAMMAD, MS, MPH

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PAMELA E. SCOTT, PhD, MA

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SOLOMON IYASU, MD, MPH

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MELISSA S. TASSINARI, PhD, DABT

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VICKI MOYER, MS

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MICHAEL D. NGUYEN, MD

10

LYNNE YAO, MD

11

LEYLA SAHIN, MD, FACOG

12

13 *Appearing via telephone.* * * * *

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Food and Drug Administration Public Meeting 05-28-2014

4

1	C O N T E N T S	
2	Welcome and Introduction	6
3	Vicki Moyer, MS	
4	Senior Regulatory Project Manager, Pediatric and Maternal Health Staff	
5	(PMHS), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)	
6	Meeting Objectives and Goals	8
7	Solomon Iyasu, MD, MPH	
8	Director, Office of Pharmacovigilance & Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE), CDER	
9		
10	Opening Remarks	19
11	Lynne Yao, MD	
12	Associate Director, PMHS, OND, CDER	
13		
14	Pregnancy Registries and Other Post-approval Studies Current Status and FDA Observations	26
15	Leyla Sahin, MD, FACOG	31
16	Medical Officer, PMHS, OND, CDER	
17		
18	Hoda T. Hammad, MS, MPH	31
19	ORISE Fellow, OPE, OSE, CDER	
20		
21	Clarifying Questions for the Presenters from the Panel	42
22		
23	Topic 1: Pregnancy Registries - Perspectives/Challenges Relating to Data Collection and Analyses	43
24		
25	Moderator Introduction to Topic 1:	43
26		
27	Melissa S. Tassinari, PhD, DABT	
28	Senior Clinical Advisor, PMHS, OND, CDER	
29		
30		

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

5

1	C O N T E N T S (Cont.)	
2	Study Design and Methodology	44
3	Sonia Hernandez-Diaz, MD, DrPH	
4	Director of the Pharmacoepidemiology	
5	Program and Associate Professor of	
6	Epidemiology, Harvard School of Public	
7	Health	
8	Comparison Group	67
9	Lewis B. Holmes, MD	
10	Director, North American Anti-Epileptic	
11	Drug Pregnancy Registry, Professor of	
12	Pediatrics, Harvard Medical School	
13	Multi-product Registries	92
14	Jessica Albano, PhD, MPH	
15	Sr. Director, Epidemiology, Post	
16	Approval & Strategic Services,	
17	INC Research LLC	
18	Data Collection/Experience with Vaccines	108
19	Adel Abou-Ali, PharmD, ScD, MD	
20	Deputy Director of Global	
21	Pharmacoepidemiology and Risk	
22	Management, Sanofi Pasteur	
23	(Industry representative)	
24	Clarifying Questions for the Presenters from	123
25	the Panel	
26	Topic 1 Panel Discussion and Q&A	130
27	Moderator Wrap-up Morning Session	187
28	* * * * *	
29		
30		

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

6

1 P R O C E E D I N G S

2 WELCOME AND INTRODUCTION

3 MS. MOYER: My name is Vicki Moyer. And
4 I serve as a regulatory project manager in the
5 Center for Drug Evaluation and Research in the
6 Office of New Drugs in the Pediatric and Maternal
7 Health Staff.

8 On behalf of the Planning Committee, I
9 welcome you to this public meeting to discuss
10 study approaches and methods to evaluate the
11 safety of drugs and biological products during
12 pregnancy in the post-approval setting. Your
13 attendance and participation today in person and
14 via the webcast are sincerely appreciated. We
15 would like to thank the many individuals inside
16 and outside of FDA who have put a significant
17 amount of time and effort into bringing this
18 meeting to fruition.

19 Before we begin, I would like to share a
20 few housekeeping details. Please silence your
21 cell phones and Blackberries and other devices.
22 Please check in at the tables outside the lobby if

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Food and Drug Administration Public Meeting 05-28-2014

7

1 you have not done so already. Agendas and
2 discussion questions are available at the
3 registration tables.

4 Open public comment speakers need to
5 sign in at the speaker registration table. If you
6 have not checked in at the meeting registration
7 desk, you need to do so. Otherwise, you may not
8 be able to speak during your time. If you have
9 not registered in advance to speak and would like
10 to speak, we will try to accommodate you if we
11 have extra time. Alternatively, please submit
12 your comments to the public docket.

13 The slide presentations for all of our
14 presenters will be posted on the FDA webpage with
15 the meeting announcement. Transcripts of the
16 meeting will be available approximately 30 days
17 after the meeting. We encourage you to post
18 comments to the docket, which is open until June
19 30th, 2014 for your feedback.

20 Restrooms are outside of the main
21 conference room in the back of the lobby area,
22 towards the coffee kiosk. We will have a 15-

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Food and Drug Administration Public Meeting 05-28-2014

8

1 minute break at around 9:45 in the morning and
2 also one around 3:20 in the afternoon. Lunch will
3 be at noon. At the kiosks in the lobby, coffee
4 and other refreshments are available for purchase
5 during the breaks and lunch hour.

6 Before proceeding with our first
7 speaker, I will provide the panel members with
8 some instructions and ask them to introduce
9 themselves. During the meeting, please remember
10 to turn on and speak into the microphones every
11 time the moderator recognizes you to speak and
12 turn them off when you're not speaking. Clearly
13 state your name each time before you speak since
14 the meeting will be transcribed.

15 Now I would like to introduce Dr.
16 Solomon Iyasu, who will be our first speaker.

17 MEETING OBJECTIVES AND GOALS

18 DR. IYASU: Good morning. It is my
19 pleasure to welcome you on behalf of CDER and FDA
20 to this public workshop, which is really a very
21 important activity that we have been concerned
22 about for some time. And so Dr. Kweder, who is

1 actually the deputy director, is running late. So
2 maybe if she arrives in time, she might want to
3 give some remarks. But for the purpose of the
4 first introduction into this subject area, I just
5 wanted to lay out sort of what the needs are and
6 what we are gathered to do during the next day and
7 a half.

8 So the topic for discussion today is
9 "Study Approaches and Methods to Evaluate the
10 Safety of Drugs and Biological Products During
11 Pregnancy in the Post-Approval Setting." Okay. So
12 why are we here, really? As you know, human data
13 which is about medical product safety in pregnancy
14 at time of market approval is really very scant,
15 if not absent. So almost all the safety data that
16 we collect or we get about human experience is
17 really obtained in the post-approval period. Some
18 of it is because there is intentional exposure
19 because there are some conditions that require use
20 during pregnancy. So we can't really avoid it.
21 So we learn some -- we get some data from those
22 exposures or they're really for approved uses in

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Food and Drug Administration Public Meeting 05-28-2014

10

1 terms of, let's say, vaccines, where the use might
2 be indicated in pregnant women. So there are data
3 that are collected post-marketing that could be
4 useful, to understand, the safety profile of the
5 medical product.

6 There is also unintentional exposure to
7 products that happens in the post-market period.
8 As you know, you know, about 50 percent of
9 pregnancies are unplanned. So there has got to be
10 unintentional and also accidental exposure to
11 medical products during pregnancy, even before
12 pregnancy is recognized.

13 So let me just go over a little bit of
14 the history. I think, you know, the first
15 guidance that FDA published on pregnancy
16 registries was in 2002. In that guidance, we say
17 that we could request studies, primarily pregnancy
18 registries, of sponsors to understand the safety
19 profile of drugs if we have a question that is of
20 concern.

21 And generally there was voluntary
22 participation by pregnant women into these

1 registries. We specified that they should be
2 prospective so that outcomes are collected later
3 on; that is, the data collection about exposures
4 and other covariates should be done before the
5 outcome of pregnancy is known -- so that's what we
6 call prospective -- and that we should have a
7 valid reference population or comparator group to
8 compare it to.

9 So these are some of the main pillars of
10 this pregnancy registry, the request that we have
11 been issuing for several years. But things
12 changed in 2007 under FDAAA, which is the
13 legislation that provided FDA authority to
14 require studies if we have this prior knowledge
15 based on pharmacological chemical class or animal
16 data or clinical trial data about a potential
17 safety issue of a serious nature if a drug is used
18 during pregnancy.

19 The other trigger might be that the
20 product is indicated for use in pregnancy as
21 vaccines or drugs for chronic conditions. And
22 another possibility or reason or trigger for

1 requiring studies might be that there is a high
2 likelihood of use in females that are of
3 reproductive age such that inadvertent exposure
4 during pregnancy may be expected. So in those
5 conditions, FDA does have the authority to require
6 studies to be conducted by sponsors.

7 Well, what has been our experience to
8 date with pregnancy registries? I think we have
9 had many pregnancy registries that have been
10 implemented. There have been some successes.
11 There have been some failures. So part of the
12 focus of today's discussion will be really to
13 collectively look over what our experience has
14 been in terms of what has been successful, what
15 have we gotten out of registries, how can they be
16 improved. So the next talk after me actually will
17 be an FDA presentation by Dr. Leyla Sahin and also
18 Hoda Hammad, who would be talking about our
19 experience from an exploratory analysis of
20 experience of registries from the FDA context,
21 sort of from our perspective.

22 We have not been really only restricted

1 to pregnancy registry. We have had some
2 initiatives also to try to sort of expand our
3 ability to address issues of pregnancy exposures
4 and safety. And one of those programs is what we
5 call Medication Exposure in Pregnancy Risk
6 Evaluation Program, which is an attempt to link
7 exposure data during pregnancy with outcomes,
8 which means linking it to the birth certificate
9 and other records. And so there would be actually
10 a presentation about this experience also. I
11 think it's the second day of our program.

12 And then there have been a number of
13 other federal efforts as well. And I think there
14 will be some talk that has been given about the
15 other federal efforts, including the DOD. And
16 also we will be looking at what opportunities
17 there are using or leveraging such databases.
18 There are also other approaches that will be
19 discussed, which will be a focus, really, for the
20 second day of the workshop, which is really
21 talking about alternative methods beyond pregnancy
22 registries, which is really an important activity.

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Food and Drug Administration Public Meeting 05-28-2014

14

1 I think there are a lot of data and opportunities
2 that can be taken advantage of from really
3 thinking about how we can make them better, how
4 can we leverage those databases, the methodologies
5 to really inform safety during pregnancy.

6 So, as I say, the main focus is really
7 on pregnancy registry but allotting a whole half-
8 day, really, on alternative methodologies beyond
9 pregnancy registries. So those are the two areas.
10 So we're trying to gather as much input and
11 suggestions from a wide variety of folks here,
12 including regulators, researchers, pharmaceutical
13 industry, the public health agencies, health care
14 providers and the public. So you really represent
15 a wide spectrum of stakeholders today. And we're
16 really eager to hear about your views and about
17 the experiences about implementing pregnancy
18 exposure registries with respect to really
19 understanding the safety profile and medications
20 and other products within pregnancy.

21 And then the second is really, as I say,
22 alternative complementary approaches. I mean, we

1 are not saying that we are abandoning the whole
2 effort of doing pregnancy registries but how can
3 we really complement that effort with other
4 methodologies and other databases?

5 So the meeting objectives are really to
6 understand the current status of pregnancy
7 exposure registries and identify successes and
8 challenges and also identify strategies to improve
9 the design and conduct of pregnancy registries so
10 that, you know, we get the data that it will be
11 important that would inform labeling, at least
12 from a regulatory perspective but also provide
13 information to patients and prescribers about
14 rational use of medications during pregnancy.

15 We also want to get some ideas and input
16 about best practices for outreach and
17 communication about implementation of pregnancy
18 registries. And that's an area that we're very
19 concerned about. The fact that you have a
20 pregnancy registry out there or maybe it's
21 included in the label may not be enough. So what
22 are the other ways of really doing some metrics so

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16

1 that enrollment and retention and also success of
2 conducting the registries become a reality?

3 Then the last is alternative post-
4 marketing approaches for assessing medical product
5 safety.

6 So today, really, a lot of the focus
7 would be on pregnancy exposure registries and
8 post-approval data, which will be really starting
9 us off with a discussion about pregnancy
10 registries. That will be the FDA presentation I
11 talked about. And then the topic 1 presentation,
12 followed by a panel discussion about pregnancy
13 exposure registries' perspectives/challenges from
14 the real world on data collection and analysis.
15 And the speakers and the panel questions are in your
16 package for that.

17 This will be followed by an open public
18 comment. And then later in the afternoon, we will
19 have a specific discussion about enrollment,
20 retention, and communication regarding pregnancy
21 registries.

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17

1 Tomorrow will be topic 3 and topic 4. So
2 we'll be focusing entirely in the morning about
3 alternative approaches, which will be followed
4 again by an open public comment. And then the
5 last session will be really how to move forward
6 because, after all, the discussions and the input
7 and the recommendations will be the next steps
8 that we need to embark on specifically about
9 moving forward in the field so that we have,
10 actually, a system or set of databases and
11 approaches and methods that will be really
12 advancing the science in this field. I think the
13 passion is there among everybody who is working in
14 this field, but I think we need to think beyond
15 sort of just the passion and then say, "What are
16 the ways that we can collaborate together? What
17 are the ways that we can improve the systems? What
18 are the ways that we can really inform patients
19 and also prescribers about the safe and effective
20 use of medications during pregnancy?"

21 Well, one thing that I need to emphasize
22 is that at this meeting, we're not going to be

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18

1 talking about specific products per se. So there
2 will not be any product-specific discussions. It
3 will be really about talking about how do we get
4 the methods and data that are needed to inform
5 this field and how can we improve the systems that
6 we have beyond what we have been doing for the
7 last 10 or 20 years.

8 So I would caution that there should not
9 be any discussion about specific products or
10 product-specific issues at this meeting. And I
11 think that it would really make it very helpful to
12 us that all of you actually participate. We are
13 very eager to hear not just from the panelists
14 here but also from the public who are present
15 here. There is a lot of interest. There is a lot
16 of passion in this area. So step up to the mike
17 during the open public period. And, you know, we
18 would like to hear your ideas. And we want to
19 have an open, collaborative discussion. And at
20 the end of the day, you know, FDA is going to take
21 all of these ideas that have been generated and
22 try to come up with sort of better strategies for

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Food and Drug Administration Public Meeting 05-28-2014

19

1 addressing this field.

2 So, without further ado, I am going to
3 introduce the next speaker. Oh, Lynne, you are
4 going to do some remarks? Okay. So Lynne Yao is going to
5 come to the podium and give some remarks. And she
6 is actually the director of the Pediatric and
7 Maternal Health Staff at FDA. She is within CDER.
8 So thank you for stepping up.

9 DR. YAO: Thanks, Dr. Iyasu.

10 OPENING REMARKS

11 DR. YAO: So I am pinch-hitting for
12 Sandy Kweder, who is my boss. And, unfortunately,
13 she is, we have just been told stuck with a flat
14 tire. So we'll all keep our fingers crossed that
15 Sandy can actually make it to work.

16 I really don't have any prepared
17 remarks. And I am not going to try and explain
18 what Sandy was going to say. But I do want to
19 make sure that we had a chance to introduce our
20 panelists and allow our panelists to introduce
21 themselves to each other.

22 So why don't we go ahead and start where

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Food and Drug Administration Public Meeting 05-28-2014

20

1 we would like to start? How about on this edge of
2 the horseshoe? If you could just speak into the
3 mike? You can just hit that button. You have to
4 turn it on and then turn it off. If you could
5 just tell us who you are and where you are from,
6 just a few comments about where you are from?

7 DR. DANA: Yes. Hello. Good morning. I
8 am Adrian Dana. And I work for Merck. And I have
9 been involved in product safety at Merck for the
10 last ten years. I am a pediatrician by training
11 and was in practice for many years before that.
12 Thank you so much for having us here today. I
13 think this is an important topic.

14 DR. ABOU-ALI: Good morning. My name is
15 Adel Abou-Ali. I work for Sanofi Pasteur in
16 Canada. I have been with Sanofi Pasteur for about
17 six months right now. Before that, I worked for
18 the FDA for about three months. And thanks for
19 having us here.

20 DR. CRAGAN: I am Jan Cragan from the
21 National Center on Birth Defects and Developmental
22 Disabilities at CDC. We conduct birth defect

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21

1 surveillance and research projects, including
2 outcomes related to medication use in pregnancy.

3 DR. HANSEN: Good morning. My name is
4 Craig Hansen. I am an epidemiologist. I am from
5 Center for Health Research at Kaiser Permanente
6 Georgia and also from the School of Pharmacy and
7 Medical Sciences at the University of South
8 Australia. Thank you.

9 DR. HOLMES: Good morning. I am Lewis
10 Holmes. I am here as the Director of the North
11 American AED Pregnancy Registry.

12 DR. ALBANO: Hello. I am Jessica
13 Albano. I am the Senior Director of Epidemiology
14 at INC Research. We conduct post-approval
15 studies, including pregnancy registries.

16 COL COSTER: I am Trinka Coster from the
17 Department of Army. I run the Pharmacovigilance
18 Center for the Army, where we monitor medication
19 use in prescribing practice for the Department of
20 Defense and also have established a mother-child
21 database.

22 DR. ANDRADE: Hi. My name is Susan

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Food and Drug Administration Public Meeting 05-28-2014

22

1 Andrade, an investigator at the Meyers Primary
2 Care Institute and the HMO Research Network. And
3 I have been involved with the Medication Exposure
4 in Pregnancy Program for quite a number of years
5 now. Thank you.

6 DR. CHAMBERS: I'm Tina Chambers. And I
7 am at the University of California San Diego in
8 the Department of Pediatrics. And I am an
9 epidemiologist and work with the MotherToBaby OTIS
10 Pregnancy Registries and the VAMPSS system.

11 DR. SCOTT: Hi. I am Pamela Scott. I
12 am the Director of Research and Development for
13 the Office of Women's Health. I am an
14 epidemiologist and a statistician by training. I
15 am the former lead for FDA's Medication Exposure
16 in Risk Evaluation Program. Currently I am in the
17 Office of Women's Health, where we maintain and
18 manage the FDA pregnancy registry webpage and
19 other pregnancy-related outreach activities.

20 DR. IYASU: Yes. My name is Solomon
21 Iyasu. I am the Director of the Office of
22 Pharmacovigilance and Epidemiology in the Center

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Food and Drug Administration Public Meeting 05-28-2014

23

1 for Drugs.

2 DR. TASSINARI: Good morning. I am
3 Melissa Tassinari. I am a senior clinical adviser
4 in CDER, Office of New Drugs, the Pediatric and
5 Maternal Health Staff.

6 MS. MOYER: Good morning. I am Vicki
7 Moyer. I am the senior project manager in the
8 Pediatric and Maternal Health Staff.

9 DR. NGUYEN: Good morning. I am Michael
10 Nguyen. I am a pediatrician by training and the
11 Acting Director for the Division of Epidemiology
12 in CBER.

13 DR. SAHIN: Good morning. I am Leyla
14 Sahin. I am a medical officer with the Pediatric
15 and Maternal Health Staff in the Office of New
16 Drugs in CDER. I practiced ob-gyn for 12 years
17 before coming to the agency 6 years ago. Thank
18 you.

19 DR. HERNANDEZ-DIAZ: Sonia Hernandez-
20 Diaz, Associate Professor of Epidemiology at
21 Harvard School of Public Health. And my research
22 focuses on the safety of medication during

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Food and Drug Administration Public Meeting 05-28-2014

24

1 pregnancy.

2 DR. BERLINER: I am Elise Berliner from
3 the Agency for Healthcare Research and Quality. I
4 am the Director of the Technology Assessment
5 Program. I work with the Medicare coverage group.
6 And because of their interest in coverage with
7 evidence development and registries, a bunch of
8 years ago, they asked us what we could do to help
9 advance the methods and science of registries. So
10 we have now just published the third edition of
11 the AHRQ handbook on the users' guide on
12 registries. And the third edition actually has a
13 chapter now on pregnancy registries. And we have
14 also started the registry of patient registries.

15 DR. GREENE: I'm Mike Greene. I'm an
16 obstetrician-gynecologist at Massachusetts General
17 Hospital. I practice maternal/fetal medicine. I
18 am Director of Obstetrics there.

19 MS. JOHNSON: I'm Diana Johnson. And I
20 am a study manager for the OTIS pregnancy studies.

21 DR. MITCHELL: I'm Allen Mitchell,
22 Director of the Slone Epidemiology Center at

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25

1 Boston University and the PI on the Birth Defects
2 Study and also part of the VAMPSS system.

3 DR. YAO: In addition, we have a few
4 participants over the telephone who couldn't
5 actually make it to our lovely White Oak campus
6 this morning. And I would have Dr. Ava Marie
7 Conlin. I think you're on the phone. Can you
8 hear us? And could you say hello this morning?

9 DR. CONLIN: I am on the phone. Thank
10 you so much for having me. It's quite early here
11 in San Diego, California. My name is Ana Marie
12 Conlin. I am a preventive medicine physician. And
13 I am at the Naval Health Research Center, where we
14 led the Department of Defense Birth and Infant
15 Health Registry. I am also principal investigator
16 for a smallpox vaccine in pregnancy registry and
17 an anthrax vaccine in pregnancy registry.

18 DR. YAO: Great. And also on the
19 telephone, we have Dr. Peggy Honein. Dr. Honein,
20 can you hear us? And can you introduce yourself?

21 DR. HONEIN: Yes. This is Dr. Peggy
22 Honein from the Centers for Disease Control Birth

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Food and Drug Administration Public Meeting 05-28-2014

26

1 Defects Branch. I'm an epidemiologist.

2 DR. YAO: Great. And lastly we have Dr.
3 Alison Naleway, who won't be able to join us this
4 morning, but we are hoping that she will be able
5 to join us this afternoon.

6 So thank you all, panelists, for
7 introducing yourselves. We are really excited
8 about the next day and a half. And we think, we
9 hope, and we expect, that we'll get much needed
10 advice to help lead the way in terms of the next
11 chapter in pregnancy exposure registries.

12 And, with that, I would like to
13 introduce our first speaker of the morning, Dr.
14 Leyla Sahin; as she has introduced herself, a
15 medical officer and reviewer and on our staff at
16 the Pediatric and Maternal Health Staff in CDER.
17 Come on up, Leyla.

18 PREGNANCY REGISTRIES AND OTHER
19 POST-APPROVAL STUDIES CURRENT STATUS AND FDA
20 OBSERVATIONS

21 DR. SAHIN: Vicki, I might need some
22 help over here. Oh, here we are. Okay. All

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Food and Drug Administration Public Meeting 05-28-2014

27

1 right. Good morning, everybody. Today's talk
2 will include some background information, some
3 information on the regulatory history of post-
4 market data collection in pregnant women. We'll
5 provide an update on the current status of
6 pregnancy registries. We'll also present some
7 results from an exploratory review of pregnancy
8 registries that we recently conducted. Hoda
9 Hammad, an ORISE fellow in the Office of
10 Surveillance and Epidemiology, will start by
11 presenting the methodology of the review. And
12 then I will present a summary of
13 preliminary results. And then I'll also mention
14 some of our observations about the results and
15 then close with some summary comments.

16 Because pregnant women are usually
17 excluded from clinical trials of investigational
18 products, at the time of approval of new drugs and
19 biologics, there are often no human data to inform
20 safety during pregnancy. Data collection in
21 pregnant women is usually performed post-approval.
22 And this is the focus of this public meeting. We

1 recognize the importance of collecting
2 pharmacokinetic and efficacy data in pregnant
3 women when appropriate, but these topics will not
4 be discussed. Collecting lactation data is also
5 important, but this will not be discussed either.
6 Collecting safety data to inform use of drugs and
7 biologics in pregnancy is an important public
8 health issue, not only for FDA and regulated
9 industry but also for researchers; other federal
10 agencies; health care providers; professional
11 organizations; and, of course, patients.

12 Here's a timeline of the regulatory
13 history of post-market data collection in pregnant
14 women. In 2002, in an effort to standardize
15 industry's approach to post-market data collection
16 in pregnant women, the agency published the
17 pregnancy exposure registry guidance, which
18 includes recommendations regarding the conduct and
19 design of pregnancy registries. In 2007, passage
20 of the FDA Amendments Act gave the agency enhanced
21 authority to require safety labeling changes and
22 post-marketing studies to evaluate a safety issue.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

29

1 In 2008, the proposed and lactation labeling rule
2 published, which when finalized will change the
3 format and content of pregnancy and lactation
4 labeling and eliminate the pregnancy letter
5 categories. The final rule will also improve data
6 collection in pregnant women as information on a
7 pregnancy registry, if one exists, will be
8 included in a prominent position in the pregnancy
9 section of labeling.

10 So where are we in 2014? The pregnancy
11 registry guidance is now over ten years old. And
12 the agency is planning to make revisions. Input
13 received at this public meeting along with public
14 comments received will be considered in revising
15 the guidance.

16 The current status of pregnancy
17 exposure registries is that they are the most
18 common type of post-approval study in pregnant
19 women required or requested by the FDA as a post-
20 marketing requirement or commitment issued at the
21 time of approval or after approval if there is a
22 safety issue that has been identified. However,

1 the agency has had a concern that pregnancy
2 exposure registries often fail to provide useful
3 information, usually due to low enrollment. Often
4 these studies are open for several years with
5 little accrual of patients.

6 As described in the pregnancy registry
7 guidance, factors that may affect the successful
8 implementation of a pregnancy registry include the
9 prevalence of the disease in females of
10 reproductive potential; usage of the drug after it
11 has been approved for marketing; awareness about
12 the registry on the part of health care providers
13 and patients; and collaboration among those who
14 conduct a registry in terms of expertise and
15 involving experts in birth defects research, such
16 as the CDC and others; collaboration in terms of
17 resources and leveraging existing infrastructure
18 and systems may also help with the successful
19 implementation of a pregnancy registry.

20 In preparation for this public meeting,
21 we conducted an exploratory review to evaluate pregnancy
22 exposure registries and their ability to assess

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

31

1 safety of medical products in pregnancy and to
2 describe the characteristics of pregnancy exposure
3 registries that have provided clinically
4 meaningful data and those that have not so that we
5 could have a better understanding of where there
6 is room for improvement and learn from the
7 successes.

8 The study team members included
9 epidemiologists and medical officers across CDER
10 and CBER and across offices and divisions.

11 I will now turn it over to Hoda Hammad,
12 an ORISE fellow in OSE, who will describe the
13 methodology.

14 DR. HAMMAD: Thank you, Dr. Sahin. Good
15 morning, everyone. My name is Hoda Hammad. And I
16 am an ORISE fellow working with Dr. Sahin and the
17 FDA study team on this project. I'll be
18 describing the study methods we used for our
19 exploratory analysis of selected pregnancy
20 exposure registries.

21 In order to describe and evaluate
22 current pregnancy registries and their ability to

1 assess safety of medical products when
2 administered to pregnant women, we chose a
3 selected sample based on the list of pregnancy
4 registries on the FDA Office of Women's website.
5 We considered the sample to be broadly
6 representative, although not necessarily
7 comprehensive, and that it includes a wide variety
8 of pregnancy exposure registries. We extracted
9 data from the website starting in January 2014 and
10 evaluated 59 medical products in all. We did not
11 do a systematic review of the disease-based
12 registries for logistical reasons as some of these
13 registries contained hundreds of medical products,
14 but we do have medical products that were analyzed
15 from a variety of disease-based registries.

16 Here you can see a screenshot of the
17 Office of Women's Health website where we
18 extracted the pregnancy registry data.

19 While it is difficult to ascertain with
20 certainty whether particular study results or
21 communication efforts have the desired effect of
22 informing clinical practice, we looked at these

1 four outcomes or milestones and considered them to
2 be potentially associated with registry
3 effectiveness for the purpose of this analysis.

4 The first thing we looked for was if
5 there was a labeling change where the registry
6 results were included in the product insert. Once
7 we collected more information about each medical
8 product, we looked to see if there was a stated
9 target enrollment and if the stated target
10 enrollment was achieved. We also looked to see if
11 there were any references to data from the
12 registry in clinical practice guidelines or if
13 there were any publication of registry results in
14 peer-reviewed journals.

15 In order to determine if any of the
16 pregnancy registries had the outcome measures we
17 were looking for, we conducted an extensive search
18 of internal FDA databases. This included any
19 protocols, reports, final study reports, or
20 clinical reviews by FDA staff. We also looked at
21 approved product labeling on the Drugs@FDA
22 website to determine the history of product

1 labeling changes regarding safety of exposure
2 during pregnancy. After that, we looked for any
3 drug safety communications on the FDA Drug Safety
4 Communications website. We also searched through
5 electronic bibliographic sources to identify if
6 there are any peer-reviewed publications which
7 describe pregnancy registry results or if any
8 provided recommendations for clinical practice or
9 if other study methods were conducted by other
10 researchers.

11 For data analysis, we used descriptive
12 statistics to describe key features and
13 characteristics we are interested in, including
14 frequency counts and proportions. We stratified
15 the data several different ways, including whether
16 the registry resulted in labeling changes that
17 were included in approved product labeling,
18 whether the registry results were published in a
19 peer-reviewed journal or peer-reviewed articles,
20 and whether the registry reached target
21 enrollments. Extensive quality assurance checks
22 were also conducted by the core data analysis team

1 to ensure accuracy and completeness of the data
2 for the key fields, which were specified for
3 analysis. All the analyses were performed using
4 SAS version 9.3.

5

6 So some of the registry characteristics
7 we chose to focus on included time period of
8 initiation of the registry, if it was started
9 before or after the FDA guidance was published in
10 2002 or if it was started before or after FDAAA
11 took effect in 2007. We also looked at if the
12 indication for use of the medical product
13 evaluated in the registry was a rare disease; if
14 the registry included one medical product or
15 multiple medical products; if it was implemented
16 as a post-marketing requirement, a post-marketing
17 commitment, or neither; if it was required under
18 a risk evaluation and mitigation strategy, REMS;
19 or whether the information about enrolling in the
20 registry was included in the approved labeling;
21 and if the registry includes patients from the
22 United States only or from other countries.

1 Now I will turn the podium back to Dr.
2 Sahin, who will describe some of the results of
3 our analysis. Thank you.

4 DR. SAHIN: Thank you, Hoda.

5 Fifty-nine products from 38 pregnancy
6 registries were evaluated, consisting mostly of
7 drugs, followed by biologics and then vaccines.

8 The proportion of registries that were a
9 PMR or PMC was pretty similar to the proportion of
10 registries that were not a regulatory obligation.

11 Seventy-six percent of products have registry
12 enrollment information included in approved
13 labeling. Fifty-three percent of products have
14 registries that are U.S.-based only.

15 The duration of the registry was less
16 than 5 years in 41 percent of the products, 5 to
17 10 years in 39 percent, and greater than 10 years
18 in 20 percent.

19 In terms of pregnancy registry data that
20 contributed to a labeling change, there were seven
21 products. And these included Truvada,
22 tenofovir/emtricitabine, based on data from the

1 Antiretroviral Pregnancy Registry; bupropion based
2 on data from the Bupropion Pregnancy Registry;
3 Singulair, montelukast, based on data from the
4 pregnancy registry of the same name; Varivax,
5 Proquad, and Zostavax vaccines based on data from
6 the Pregnancy Registry for Varicella Zoster Virus-
7 Containing Vaccines; and Mycophenolate based on
8 data from the National Transplant Pregnancy
9 Registry.

10 Here is an example of approved labeling
11 informed by pregnancy registry data. This is from
12 December of 2013. As we wait for the final
13 Pregnancy and Lactation Labeling Rule to go
14 through clearance and publish as a final rule, we
15 have been encouraging companies to submit labeling
16 in the new format. And here you can see the three
17 new sections which consist of the risk summary,
18 clinical considerations, and data. Data from the
19 international Bupropion Pregnancy Registry are
20 presented under the data section.

21 Here is another example of approved
22 labeling informed by pregnancy registry data. And

1 this is from 2012. This is also in the new
2 format. As you can see, the pregnancy registry
3 information is presented first. And the data from
4 the Antiretroviral Pregnancy Registry are
5 presented at the bottom of the slide.

6 For the seven products with registry
7 data added to approved labeling, results were also
8 published in a peer-reviewed journal for six.
9 Overall, for the total 59 products, interim or
10 final registry results were published in a peer-
11 reviewed journal for 22.

12 Pregnancy registry data for the
13 following seven products contributed to clinical
14 practice guidelines: Humira, adalimumab, based on
15 data from the Organization of Teratology
16 Information Specialists, OTIS, Autoimmune Diseases
17 Study; Gardasil, Human Papillomavirus Quadrivalent
18 Vaccine, based on data from its pregnancy
19 registry; Viread, tenofovir, and Truvada based on
20 data from the Antiretroviral Pregnancy Registry;
21 Varivax, Proquad, and Zostavax Vaccine based on
22 data from the Pregnancy Registry for Varicella

1 Zoster Virus-Containing Vaccines.

2 In terms of target enrollment, 22 of 59
3 products had a target enrollment stated in the
4 protocol. And of these, three achieved a target
5 enrollment.

6 In terms of registry status, 71 percent
7 of products are still part of an ongoing registry.
8 Seventeen percent are closed for feasibility
9 reasons, most commonly due to low enrollment. And
10 12 percent are closed and considered completed.

11 Information about loss to follow-up of
12 the registry's pregnancy outcome data was
13 available for 32 of the 59 products. After
14 excluding registries with low enrollment(less
15 than 20 patients), the loss to follow-up rate was
16 calculated for the remaining 21 products, with a
17 median loss to follow-up rate of 23.4 percent,
18 with a range of 1.6 to 52.7 percent and an
19 interquartile range of 3 percent to 36 percent.

20 Some alternative approaches that were
21 identified during the review that either
22 contributed to labeling, were conducted or funded

1 by industry, or published in the literature
2 include case control studies, cohort studies,
3 claims database studies, case series and reports,
4 European national birth register data, passive
5 surveillance, enhanced pharmacovigilance, and
6 inadvertent exposures during product development.

7 Some of the limitations of this
8 exploratory review are listed on this slide. It
9 did not include a systematic review of the six
10 disease-based registries listed on the Office of
11 Women's Health webpage, although some products
12 from some of these registries were included in the
13 review.

14 It is not a comprehensive review of all
15 pregnancy registries. It did not assess pregnancy
16 registry data quality or methodology or other
17 factors that may contribute to the successful
18 conduct of a registry, such as resources,
19 expertise, etcetera. It also did not assess
20 factors that affect the decision to add pregnancy
21 registry data to labeling.

22 So what does all of this mean? The

1 exploratory review suggests that pregnancy
2 registries have contributed safety data for use in
3 labeling and clinical guidelines and also
4 published in the medical literature. However,
5 there is room for improvement. And there is a
6 need to develop strategies to improve the conduct
7 of pregnancy registries. And we look forward to
8 hearing from the panel about this.

9 We are unable to draw conclusions using
10 this exploratory study on characteristics that
11 result in a successful registry. Study methods
12 and sources of data other than pregnancy
13 registries also contributed to informing risk.

14 In summary, pregnancy exposure
15 registries by themselves may not be sufficient to
16 collect data that inform product labeling. And we
17 need to explore complementary study methods, which
18 will be discussed tomorrow. Our goal is to
19 improve health outcomes for pregnant women. And
20 data collection in pregnant women is a shared
21 responsibility among all stakeholders.

22 Thank you for your attention. And I

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

42

1 would be happy to take questions.

2 MS. MOYER: Does anyone on the panel
3 have questions for Leyla or Hoda or Solomon?

4 DR. SAHIN: Yes? Go ahead, Michael.

5 CLARIFYING QUESTIONS FOR THE
6 PRESENTERS

7 FROM THE PANEL

8 DR. GREENE: I would like to just make
9 an observation about the criteria that you used
10 for the impact of the registries. One of them was
11 whether the registry met their criterion for
12 enrollment for the size of the registry. In some
13 cases, some of the registries' activities are to
14 publicize the fact that these drugs should not be
15 used during pregnancy. And the fact that fewer
16 and fewer women have been exposed to the drugs
17 actually may be a mark of the success of the
18 registry in that they don't meet their criteria
19 for enrollment because the word has gotten out
20 that the drug shouldn't be used during pregnancy.

21 DR. SAHIN: Thank you. Thank you for
22 your comment. Yes? I agree with your comment,

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

43

1 Dr. Greene. Thank you.

2 DR. TASSINARI: I think the challenge is
3 going to be, though, how do we capture that
4 because, you know, I think it is one of the points
5 that we have to have suspected, but I don't know
6 that we have documented it.

7 DR. GREENE: It's a little bit like
8 knowing when the dog didn't bark.

9 MS. MOYERS: Any questions on the phone?

10 DR. TASSINARI: No lights are on. Very
11 good.

12 TOPIC 1: PREGNANCY REGISTRIES -
13 PERSPECTIVES/CHALLENGES RELATING TO
14 DATA COLLECTION AND ANALYSES

15 MODERATOR INTRODUCTION TO TOPIC 1

16 DR. TASSINARI: Well, I guess, then,
17 what we shall do is move into our first topic. We
18 have a series of presentations this morning that
19 we hope will provide us some information to look a
20 little more closely at where we are today with the
21 pregnancy exposure registries and how the
22 different perspectives for data collection have

1 served us. I think Leyla has given you a little
2 bit of a preview of where this is going, but we
3 have specifically asked for some presentations to
4 try and round out our perspectives on the current
5 status of our data collection methods,
6 particularly with pregnancy exposure registries.

7 So, with that, we would like to start
8 with our first presentation. Dr. Sonia Hernandez-
9 Diaz is going to speak to us about study design
10 and methodology. Sonia?

11 STUDY DESIGN AND METHODOLOGY

12 DR. HERNANDEZ-DIAZ: Hi. Good morning.
13 Thank you for inviting me to be here today.

14 As a disclosure, I have consulted for
15 some pregnancy registries as an adviser. And I am
16 the epidemiologist for the Anti-Epileptic
17 Pregnancy Registry with Dr. Lew Holmes.

18 What I am going to do is to first give
19 you an introduction to study designs, just a brief
20 roadmap of some of the designs we are going to see
21 in these next two days. And then I am going to
22 focus on some specific methodological aspects for

1 pregnancy registries, including validity and
2 efficiency, or power, aspects.

3 So, as an introduction, following an
4 instructor that I learned from, Dr. Allen
5 Mitchell, we can look at study designs for safety
6 during pregnancy in two groups. One is in
7 premarketing preapproval. We have some
8 toxicological studies that are useful for us, but
9 for teratogenicity and other effects in the fetus
10 and in children as well they are usually poor
11 predictors. We also have animal studies, but
12 because of the variation of teratogenicity among
13 different species sometimes are poor predictors
14 for humans as well. And we have some clinical
15 trials that typically exclude pregnant women. And
16 that can take us to a whole different interesting
17 discussion about the ethics of that.

18 So for pregnancy information, we are
19 left with the post-approval studies. And there
20 are some clinical trials. Some large trials might
21 include, mainly inadvertently, some pregnancy women.
22 And they can provide some information, but they

1 typically provide information on a handful of
2 pregnant women. So they are not enough. So we
3 can have them post-approval, some case reports or
4 case series, sometimes under some surveillance
5 systems. But they can both provide true signals
6 but also often provide false alarms or no clues
7 about something going on.

8 We have ecological studies that can look
9 at geographical differences or trends over time.
10 And these trends are typically explained by other
11 things going on at the same time. So they are not
12 ideal either.

13 So we are left with non-experimental,
14 epidemiologic, studies for our research. And
15 there we can see both cohort studies and case
16 control studies. Within the cohort studies, some
17 of them have been designed specifically to study
18 birth defects, like the Collaborative Perinatal
19 Project. But this huge cohort even, the
20 Collaborative Perinatal Project, with over 52,000
21 women, when you want to look at a specific
22 medication and specific defects, they have a small

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

47

1 sample size, or insufficient sample size. So most
2 commonly what we do now is to have specific
3 cohorts exposed to specific medications of
4 interest. And those are the pregnancy registries
5 that we are going to discuss this morning; for
6 example, the OTIS pregnancy registries.

7 Then we have sources of four studies
8 that were not designed specifically to do research
9 or to study birth defects. There you probably
10 have seen data coming from automated claims
11 databases, such as Medicaid or HMO networks;
12 computerized medical records, like the CPRD in the
13 U.K. or here Kaiser Permanente; or pooling
14 projects that combine these resources. And we are
15 going to hear about MEPREP tomorrow.

16 For case control studies, we have some
17 that are specifically designed to study one
18 defect, but, more commonly, we have been using
19 data from case control surveillance systems, like
20 the Slone Epidemiology Center Birth Defect Study
21 or the CDC-based NBDPS Study.

22 But I am going to focus on pregnancy

1 registries. And the definition of pregnancy
2 registries is observational prospective cohort of
3 women receiving a medication of interest as part
4 of their routine clinical care who are enrolled
5 during gestation before the outcome can be known.
6 And then they are followed during pregnancy or
7 even after pregnancy to obtain information on some
8 outcomes. And then to evaluate whether that
9 frequency is as expected or higher than expected,
10 we compare them to a valid reference group.

11 As Dr. Iyasu has mentioned, the FDA has
12 some guidelines for when these registries should
13 be conducted. Right now it's when pregnant women
14 are likely to be exposed or even women of
15 childbearing age are likely to be exposed or when
16 we believe there may be a potential risk; for
17 example, vaccine. And there are some
18 recommendations as well regarding when to enroll.
19 And FDA has recommended that we want to enroll
20 women after exposure but before the pregnancy
21 outcome is known. However, if women enroll later,
22 they are also typically enrolled in the

1 registries. But it is recommended that we look at
2 them separately, at least in a sensitivity or
3 secondary analysis.

4 As a result, there are many pregnancy
5 registries. The website has been also mentioned
6 already. And I am going to use one specific
7 registry for my example because, as I mentioned, I
8 work with Dr. Lew Holmes, the principal
9 investigator of the North American Anti-Epileptic
10 Drug Pregnancy Registry. And I am going to
11 briefly go through the methods. Dr. Holmes is
12 going to talk about it more in a little bit.

13 The registry was established at the
14 Massachusetts General Hospital in Boston, 1997. It
15 enrolls pregnant women exposed or using
16 anticonvulsants/anti-epileptic drugs, as well as a
17 reference group of friends and family members that
18 are pregnant but not exposed to anticonvulsants.
19 Women call, enroll, and then the registry obtains
20 the consent. And then outcomes are validated with
21 medical records.

22 Information is obtained through three

1 interviews: one at the enrollment, one at seven
2 months gestation, and one around two months
3 postpartum. And the interviews ask questions on
4 anticonvulsants as well as some demographic, the
5 indication, epilepsy or others, vitamin use,
6 smoking, et cetera. And for every anticonvulsant
7 reported, detailed information is obtained on
8 those and on timing of use.

9 The registry considers two groups. The
10 pure prospective refers to women who enroll before
11 they had a prenatal test. And the so-called
12 traditional prospective refers to participants who
13 have enrolled after having had an informative
14 test, like amniocentesis, chorionic villus sample,
15 et cetera.

16 So I am going to go and focus on the
17 methodological points. Dr. Holmes will talk more
18 about the selection of comparison groups. I am
19 going to discuss the issues pertaining to the
20 enrollment in the registries.

21 In a typical registry, you can worry
22 about women having pregnancy losses or ending

1 pregnancy at different times. If you were
2 assessing, for example, prematurity. And those
3 programs are important and affect not only
4 pregnancy registries but any study evaluating
5 birth defects. If you are missing terminations or
6 miscarriages, then we are concerned about the
7 potential implications, but where I am going to
8 focus is on what is called in epidemiology left
9 truncation, meaning that it's the time of
10 enrollment where we can also have women enrolling
11 at different times. And that's what these lines
12 represent. The course represents just women that
13 may be exposed to different medications or exposed
14 and unexposed, being from the reference group. So
15 this is data from the registry, just a random
16 sample.

17 And here we have women enrolling around
18 the second or third month of pregnancy typically,
19 but there are some that are enrolling a little bit
20 later. You have to remember that women have to
21 recognize they are pregnant, go through their
22 neurologist, and then be referred to the registry

1 or sometimes they find information on the website.
2 So, as a result, we have women enrolling at
3 different times.

4 What can be the implications of that? So
5 the answer is that it depends on what you want to
6 study. We will all agree that if we were studying
7 infertility or problems with contraception, we
8 would have to enroll women before pregnancy.
9 Otherwise, if we were to enroll pregnant women, we
10 could not study effects on fertility.

11 So the same thing for pregnancy losses
12 or miscarriages. If that's the aim of the study,
13 we cannot enroll women at 20 weeks of pregnancy
14 because by definition, they didn't have
15 miscarriage.

16 And what about when we are interested in
17 the health of the offspring, often major
18 malformations? If that's the case, if the outcome
19 of interest is birth defects, then because we
20 currently believe that the ecologically relevant
21 period is the first trimester, we have to make
22 sure that we enroll women ideally before the first

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

53

1 trimester. What would happen if we don't do that?
2 Keep inKeeo in mind that when you are doing a registry, what
would
3 you expect to find if subjects are enrolled late
4 in pregnancy, after prenatal screening and you
5 have subjects to enroll and she had already a
6 pregnancy test and there is a problem, a potential
7 problem, with the fetus? Well, if there is a
8 diagnosis and you include the women in the
9 registry, you may be overestimating the risks
10 because perhaps women after having a diagnosis
11 will tend to look for information on enrolling in
12 the registry.

13 However, you have a call from a woman
14 and she had a diagnosis and you exclude these
15 women that call with a diagnosis. You will be
16 selecting a cohort in your registry without
17 problems. So by enrolling after prenatal
18 screening, at least for some defects, you may have
19 to live with this situation.

20 And what about this other related
21 problem? You have groups of exposed, and then you
22 have a reference group. What would you expect to

1 find if exposed subjects are enrolled during the
2 first trimester or before the prenatal screening
3 but the unexposed group is enrolled after, later
4 in pregnancy? And these graphs try to represent
5 that situation. In red here, we have the exposed
6 women, exposed to your medication of interest. And
7 then you have the reference group of unexposed.
8 If ideally all of them were enrolled in the
9 registry at conception, then some of them will
10 have, some pregnancies will have, an infant with a
11 birth defect that we can sometimes diagnose early
12 on. Sometimes we will not diagnose until
13 delivery.

14 But keep in mind now that in the unexposed
15 group, women were to enroll later. Then we could
16 argue that those women who had diagnosis and
17 perhaps even a termination and you ask them to
18 volunteer for a registry that is not about a
19 medication they are taking, they may not be in the
20 mood to enroll in the pregnancy registry if they
21 had a termination. If that is the case, then, as
22 a result, you will be selecting women

1 preferentially without a birth defect. This is
2 the theory. Now let me show you some real data
3 from the North American Anti-Epileptic Drug
4 Pregnancy Registry.

5 This graph here represents the
6 enrollment time in gestational age at enrollment
7 for women who call the registry and were on
8 anticonvulsants/anti-epileptic medications, here
9 the dark lines.

10 Just as an example, I was also providing
11 just specifically that the distribution of
12 enrollment time for two of the anticonvulsants,
13 lamotrigine and valproic acid, just to give you an
14 example. And, as you can see, there are no
15 differences when we look at the specific drugs.
16 However, in the unexposed groups of friends and
17 family members, they tend to enroll a little bit
18 later, which also makes sense. For you to invite
19 a family member or a friend to enroll in the
20 registry where you already enrolled, you have to
21 know that she is pregnant and know easily. Unless
22 this person is very close to you, that might take

1 some weeks. So that's not an unexpected
2 situation.

3 Then, just for this presentation, we
4 look at data for spontaneous abortion, even when
5 that is not one of the main outcomes for the
6 registry, but sometimes companies are required to
7 present data on spontaneous abortion.

8 So we found that overall in all
9 anticonvulsants, 353 out of 7,000 exposed had
10 miscarriages and among the nonusers a much lower
11 risk: 6/581. If you use good, simple,
12 unconditional logistic regression without
13 considering time at enrollment, that would be a
14 fivefold increased risk. If we take into account
15 when women were enrolled and compare women that
16 were enrolled at the same time at the trimester
17 level, the relative risk will go down to 2.7; if
18 we go to the Greek level, a twofold increased
19 risk. If we were to use a summary incidence rates
20 ratio, as you know, the risk of miscarriage
21 changes over time. So if we use this person time,
22 we will have a similar result of twofold versus

1 fivefold.

2 If we were to restrict these women to
3 prescreening and raise only prescreen for birth
4 defects, the results will not change, as you would
5 expect. So what happens with major malformations?
6 An unconditional not considering time at
7 enrollment, a relative risk for anticonvulsants
8 overall will give a threefold increase risk. If
9 we condition on the time and enrollment, the
10 results will not change. However, if we take into
11 account for malformations who enrolled before the
12 screening, the relative risks do go down to
13 twofold with wide confidence intervals. But it's
14 still supporting that there may be a difference
15 for defects overall if you don't pay attention to
16 the prescreening and post-screen.

17 So, in summary, in this registry and I
18 think in most registries, you will have enrollment
19 that spanned throughout the entire pregnancy. And
20 it may be different for the exposed and the
21 reference groups. And in our case, it wasn't
22 different for the specific medications.

1 If you are going to analyze spontaneous
2 abortions or any other early event, your results
3 may be sensitive to gestational age at enrollment.
4 To analyze major malformations, your results may
5 be sensitive to whether the women had prenatal
6 screens before enrollment. Therefore, to minimize
7 the left truncation, we will recommend to enroll
8 women, of course, as soon as possible in
9 pregnancy.

10 If you were studying outcomes such as
11 spontaneous abortions, where the incidence is
12 changing over time, you will have to consider
13 that your exposed and reference groups have
14 comparable time at enrollment. When the events
15 may influence enrollment, like some specific birth
16 defects, through the prenatal screening, the
17 primary analysis must include only subjects
18 enrolled before this event.

19 And now I'm going to move on to a few
20 comments on power. Again, if the main outcome of
21 interest is birth defects, then we are dealing
22 with an outcome that overall has a prevalence at

1 birth of around two to three percent. If we want
2 to focus on specific malformations, then we are
3 talking about prevalences of 1 every 1,000 for the
4 most common ones, like some cardiac or oral
5 clefts.

6 If we do a power calculation, just to
7 have an idea, and we try to focus on specific
8 birth defects, for a relative risk of 20-fold,
9 here we are talking about something close to
10 Thalidomide for a huge increased risk. If we were
11 to enroll 150 exposed in a registry and, say,
12 double the number of unexposed, for a total number
13 of subjects in our cohort of 450, then we will
14 have sufficient power. For a 12-fold increased
15 risk, again, like a very strong risk but not quite
16 as 20-fold, we will double that number. For
17 something closer to reality for a strong, a
18 fivefold, increased risk in the risk of this
19 specific malformation, we are talking about 1,500
20 or more exposed in our registry.

21 And this power calculation is a
22 mathematical calculation. And, as you can see, if

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

60

1 you expect 1 out of every 1,000 births affected
2 and we said that we had 300 in the exposed, this
3 calculation allows for you to have a .3 of a
4 person with a birth defect. So it's not reality
5 but just to give you an example.

6 And, to give you a more real example, I
7 am going to present data again from the North
8 America Pregnancy Registry to give you an example
9 of our experience with lamotrigine. And this
10 table represents the sample size enrolled on
11 lamotrigine in the registry divided into 100, 100
12 more. Then we have 200. And so far now the
13 registry has a sample size for lamotrigine of over
14 1,800. So when the registry started collecting
15 information on lamotrigine in 1997 or a little bit
16 after when lamotrigine was being commonly used,
17 for the first 100 women enrolled in lamotrigine,
18 there were 2 with oral clefts. That's 20 percent.
19 If you compare that with the expected 1 per 1,000,
20 it's huge. And if you were conducting a registry
21 and you had this huge risk, what could you do? It
22 can be real; right? So you wait a little bit

1 more. You have 200 in oral cleft. That's 15
2 every 100, rather than 1 every 1,000.

3 But then you continue. And some years
4 you have none. And at the end, when you have a
5 larger sample size, now the cumulative risk is 3.9
6 per 1,000. It's still elevated but not quite as a
7 200-fold increased risk. And this graph
8 represents what you would see in terms of here in
9 the red lines the risk or the number of cases
10 divided by the number of pregnancies enrolled on
11 lamotrigine, the first 100, and then the second
12 100 enrolled. And now it is when we have over
13 1,700.

14 As you can see, at the beginning, with 2
15 cases in the first 100, the risk was 2 per 100,
16 rather than 1 per 1,000, so a huge increased risk
17 but with very wide confidence intervals. As data
18 is accumulated, the risk went down. And the
19 confidence intervals now are much narrower.

20 So I think that's a lesson learned and it is
21 not to publish too early. Of course, at that
22 time, we didn't know if it was going to go up or

1 down. But it's a lesson learned in terms of how
2 small numbers can play games.

3 So, in conclusion, to end my
4 presentation, let me review briefly the main
5 advantages and disadvantages of pregnancy
6 registries. They are prospective drug exposure
7 studies. Therefore, there is no concern with
8 recall bias. The information is typically
9 collected before the outcome.

10 By concentrating on selected
11 medications, you can increase efficiency versus
12 doing pregnancy cohorts overall and particularly
13 when you are studying uncommon drugs in relation
14 to relatively common events. They are
15 longitudinal. Therefore, you can present not only
16 relative risk but also risk differences. You can
17 interview moms and, therefore, get not only
18 prescriptions but also real intake of the pills.
19 You can study multiple exposures if you want to
20 enroll multiple drugs in your registry and
21 multiple outcomes, but those advantages come with
22 some limitations. Some registries may not be

1 representative of the population in the sense that
2 you may have volunteers or women exposed to
3 specific medications; therefore, having a specific
4 indication. So that population may not be
5 representative or comparable to the general
6 population.

7 Some registries lack a control group and
8 may rely on an external comparison group that may
9 or may not be comparable to them. Even when I
10 said they are efficient because they focus on
11 medication, still they cost time and, therefore,
12 money. They have, most of them, a short follow-
13 up. And if you are interested in late
14 development, they may not provide that
15 information. They have losses to follow-up. And
16 you have to pay attention to the potential
17 selective under-ascertainment. And they have
18 limited powers for specific birth defects, as we
19 show.

20 So those were my slides. Thank you very
21 much.

22 DR. TASSINARI: Thank you.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

64

1 (Applause.)

2 DR. TASSINARI: We have a few moments.
3 We're running a little bit ahead. If anybody has
4 a clarifying question, we can take those. Yes?

5 DR. BERLINER: Can you talk a little bit
6 more about the enrollment? So it sounds like not
7 all doctors are inviting patients to enroll and
8 that some patients are finding the registry on
9 their own. So could you talk a little bit more
10 about how that is actually happening? Like what
11 percent of doctors are actually asking patients to
12 enroll? What percent of patients are accepting
13 enrollment? How many patients are finding it on
14 their own?

15 DR. HERNANDEZ-DIAZ: Yes. Dr. Holmes is
16 the PI of the study. So he may want to go over
17 that. I'll leave it up to him. But the registry
18 is advertising in the labels. There are posters
19 and information cards sent to neurologists,
20 epidemiologists, and other clinicians that we
21 sometimes contact through our presence in
22 meetings. And I don't have the number right here.

1 I can look it up for you, the exact proportion of how
2 many women who are calling because they were
3 searching the web -- and that's certainly very
4 common -- and find the registry and call versus
5 those that are encouraged by their prescriber,
6 clinician to enroll, which I know that happens,
7 too, but I don't have the specific proportion of
8 that.

9 And, again, maybe Dr. Holmes wants to
10 comment on that. But the registry has spent
11 efforts in this marketing of the registry to
12 get to women through different methods.

13 DR. TASSINARI: I am glad you raised it.
14 And we are going to be bringing that up again this
15 afternoon after lunch because we specifically see
16 that as an issue to have some further discussion.
17 Yes?

18 DR. GREENE: Sonia, given the example
19 that you just presented, what advice would you
20 give or guidance would you give about when is the
21 time to publicize a newly recognized apparent
22 association?

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

66

1 DR. HERNANDEZ-DIAZ: Yes. That's a very
2 good question. I don't know if I have the answer.
3 I have been wondering myself. In part, I think it
4 may be a topic to discuss when we discuss
5 communication because, on one hand, you want to I
6 think report what you have for others to replicate
7 and for women to have information. And even when
8 you may have a huge confidence interval, still
9 that may be more information than nothing.
10 However, in this case, depending on how you
11 communicate and how the information is understood,
12 that's why I think it is a communication issue.
13 You can create alarms unnecessarily.

14 So I would say that if there is a way to
15 communicate without anybody running away with a
16 relative risk and saying, "20-fold increased
17 risk," I would do it. I just still think that
18 somehow it has to be public, at least for peers to
19 go and try to replicate in their other resources.
20 But, you know, it's hard to prevent them. There
21 needs to be on the following day with a 20-fold
22 increased risk. So it's a little bit dangerous.

1 And if we find a way to communicate
2 these kinds of preliminary numbers with a lot of
3 uncertainty and lack of information around it,
4 that would be great.

5 DR. TASSINARI: I'd like to come back to
6 that question when we have the larger panel
7 discussion because I think there's much to be had
8 there. Great.

9 If there are no other clarifying
10 questions, I would like to invite Dr. Lewis Holmes
11 for his presentation on comparison groups.

12 DR. HOLMES: Thank you very much for
13 inviting me.

14 COMPARISON GROUP

15 DR. HOLMES: As you can see, Sonia and I
16 work both on the same pregnancy registry. We have
17 developed our slides separately and then compared
18 them after mine had been submitted. And you will
19 see that we have got some similar ones, but we're
20 using them to make different points. I am really
21 going to focus on the issue of the comparison
22 group that we have recruited and I think is a good

1 model for the FDA to consider as it supervises
2 pregnancy registries.

3 I think the point to make in describing
4 what a pregnancy registry is, is that everyone needs to
5 remember that it is not a clinical trial. We have
6 a lot of requests for terminology and whatnot in a
7 lot of our agreements that show that a lot of
8 folks still can't get their heads around what a
9 pregnancy registry is, but it's not a clinical
10 trial. There are many variables in a pregnancy
11 registry. And this is a list of several of those.

12 We're focusing today, my comments, on
13 the last two items here: the inclusion and
14 exclusion criteria, which are a crucial part of
15 your comparison group; and then the actual
16 comparison group itself.

17 As Sonia has pointed out, there are
18 several steps in our process of enrolling a woman.
19 We enroll among women who are pregnant throughout
20 the United States and Canada. And the key issue
21 here is at the end of the interview, the research
22 assistant who is talking to the woman and using a

1 computer-assisted telephone interview tells her
2 about our desire to have her help us recruit
3 individuals who are also pregnant who are not
4 taking these medications. So it is a verbal
5 invitation at the end of the interview. And that
6 is the essential beginning of the recruitment
7 process.

8 So you have as you advise individuals
9 about pregnancy registries the two models. To me,
10 there are a lot of problems with the historical
11 comparison group. I am going to focus on the
12 internal comparison group. This is a system that
13 Caitlin Reilly Smith, who is our project manager,
14 developed early on several years ago. And now 10
15 percent of our enrollees each month -- we enroll
16 about 50 women each month, and about 10 percent of
17 them have continued to be women who are in the
18 comparison group. And, as Sonia mentioned, they
19 are friends and family members of the enrolled
20 woman.

21 First, there is the issue of the number.
22 And then there will be the issue of the specific

1 qualities of the malformation itself. One of my
2 complaints to people is of the frequency of birth
3 defects at birth is not three to five percent, as
4 a lot of people are taught, or two to four
5 percent, as Sonia showed in her slide. It really
6 depends on your definition of a malformation, how
7 you got the information, what your exclusion
8 criteria are. I'll show you later the details of
9 our exclusion criteria, but the gist of it is
10 let's start with two studies we have done where we
11 examined the children ourselves. And you can see
12 we carried out a cohort study. Unfortunately,
13 there is a typo in the year, but it was 2001 that
14 it was published.

15 These were infants born to women taking
16 anticonvulsant drugs at any of five hospitals in
17 the Boston area. We examined the children
18 ourselves with a protocol that makes you pay
19 attention to details and be consistent and a
20 rather boring thing to do. And the examiner was
21 masked as to which children was born to a woman on
22 the drugs versus a woman who was not on the

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

71

1 medication. You can see the rate was 1.8 percent.

2 Using a different approach, a
3 malformation surveillance program, which we
4 conducted at Brigham and Women's Hospital for 40
5 years, here is some data that has been published.
6 You can see that using the pediatricians'
7 findings, not our own exams, the rate was 2.24
8 percent.

9 If you subtract chromosome abnormalities
10 and dominant/recessive disorders, it gets down to
11 roughly two percent. And you can see one
12 publication from several years ago. And the more
13 complete data set is being analyzed right now.

14 Okay. Those are two of our studies
15 showing roughly a two percent rate. These are
16 other sources. They don't all give details on the
17 inclusion and exclusion criteria, but you can see
18 that there are four different major sources. Two
19 are currently active. For example, the important
20 Metropolitan Atlanta Congenital Birth Defects
21 Program, MACDP, you can see there is a rate of 2.1
22 percent at birth. It was in the paper published

1 in 2007. The other one that's currently underway
2 is Eurocat, which is a European registry-based
3 system. You can see they have 2.3 percent; 2 of
4 their older studies, similar outcomes.

5 My point is if you are talking about
6 structural abnormalities with surgical, medical,
7 or biological importance, the rate at birth is
8 roughly about two percent. And then you would
9 subtract the chromosome abnormalities and the
10 recognized genetic conditions. And you would
11 actually get slightly below that. So that is sort
12 of step number one. If you have at the FDA a
13 company submitting a proposal and it says the rate
14 in the general population at birth is two to four
15 percent, you should say, "Where did you get that
16 four percent?" Usually they have no idea of where
17 they got it, but they should have an internal
18 comparison group that would be the basis for that
19 rate.

20 These are the exclusions that we have
21 used for all our studies for these 40 years. And
22 they're published in the paper that is listed

1 there at the bottom. Anybody who examines babies
2 knows that lots of babies have a lot of little
3 diddly things that the mother may notice and may
4 want you to discuss, but they are of no great
5 significance biologically. These are extremely
6 common. The study that is cited there from Birth
7 Defects Research A showed that the frequency of
8 these minor malformations is 20 times greater than
9 the frequency of actual malformations.

10 Now let's get into the dynamics of
11 specific findings. This is not where we are
12 focusing on the rate, but you are actually saying
13 you are looking at the reports that come in from
14 the pediatricians, you are talking to the mother.
15 She is saying the child has polydactyly. Well,
16 everybody who does pediatrics and genetics knows
17 that there's polydactyly and then there's
18 polydactyly. And so you really need to be
19 specific.

20 Think of how many pregnancy registries
21 where you have seen as the outcomes the
22 publication just says, "Polydactyly." Well, I

1 listed four here. And you can see number one,
2 postaxial polydactyly, type b, extremely common.
3 One in 100 African American infants has that, 1 in
4 1,000 Caucasian infants, extremely common, is not
5 known to be associated with any exposure during
6 pregnancy. And in our system, it would be
7 excluded as an hereditary finding.

8 Then you see the other three types. The
9 one that is probably most notable is to talk about
10 the preaxial polydactyly, "preaxial" meaning, of
11 course, the thumb side, as opposed to postaxial,
12 the fifth finger side. My point is you can't just
13 list polydactyly. There needs to be someone who
14 knows birth defects, who has seen them before, who
15 is not sitting there Googling the finding to make
16 the comment on the quality or significance of that
17 information.

18 Prematurity-related findings. These
19 have become in the time since we started in 1997
20 an extremely common issue to wrestle with and
21 develop your criteria for including and excluding
22 a finding. Fortunately, a lot of prematurely born

1 infants are now surviving. Imaging is powerful.
2 These children have imaging studies over and over
3 and over during the time they are in the hospital
4 before they go home. It is very common for an
5 infant who is 28 weeks gestation to be found to
6 have, as this slide shows, a patent ductus as well
7 as a patent foramen ovale.

8 These are normal physiological findings.
9 They are not a birth defect. And, yet, when
10 people rely on ICD-9 codes, these are going to be
11 listed by the poor, hardworking coder as a birth
12 defect. One is a PDA. And the other is
13 classified as a type of atrial septal defect. My
14 point is you should be making a qualitative
15 judgment on this story and using exclusion
16 criteria that would consider the prematurity
17 issue.

18 Probably the more contentious issue that
19 we wrestle with all the time and people debate
20 when we present our findings is, what do you do
21 about findings during pregnancy by prenatal
22 ultrasound? That technology has become extremely

1 common, but there is no systematic screening done
2 among the women who enroll in our registry and,
3 for that matter, among women in general. It's lot
4 of variation from site to site in terms of the
5 quality of the equipment, when the ultrasound
6 screening is done, who is reading it, and so
7 forth.

8 So we have always maintained that if the
9 pediatrician doesn't find something at birth, it
10 doesn't count. Others argue with that, which is
11 their prerogative. And if they have an internal
12 comparison group, they can certainly include them
13 in both the exposed and the unexposed. And it
14 will all balance out.

15 We found when we have followed up on the
16 cases we have actually been told about a
17 significant number of them go away and turn out
18 not to be significant. So that would be an issue
19 to bear in mind.

20 If you were high bound and determined to
21 include things found by ultrasound, such as
22 hydronephrosis, here is what our analysis showed

1 the effect would be. This is an analysis that
2 Marie-Noel Westgate and I did of 1,000 consecutive
3 births at Brigham and Women's Hospital, where we
4 went through the medical record, Marie-Noel did,
5 identified all of the diddles that were recorded
6 by the pediatricians, the birthmarks, the minor
7 anomalies, and so forth, as well as the findings
8 reported by the mother. If you insisted on
9 including the ultrasound-only findings, primarily
10 hydronephrosis, you would essentially add to your
11 baseline rate two percent. So, in other words, if
12 the baseline rate were two percent without
13 ultrasound, you add the ultrasound only. Suddenly
14 your baseline is four percent. And, as I said, if
15 that's what you want to do and you do that in both
16 your exposed and your unexposed comparison group,
17 it all balances out and you have no problem. But
18 if you are trying to use an historical record as a
19 basis for your comparison group, how do you know
20 which of those were detected during pregnancy?

21 One of the issues that is a fact of life
22 for a pregnancy registry is how long are you going

1 to be funded? When we have started, we were
2 supported only by companies. And that is still
3 the case. And when we have findings, this is an
4 issue related to Mike's question about, when do
5 you publish? If you are not sure how long you are
6 going to be funded, you might as well if you have
7 a significant finding have the uncertainty a part
8 of your decision-making in terms of okay Let's
9 go ahead and publish this because we're not sure
10 we're going to be around when the sample size is
11 twice as big.

12 You can see from this other power
13 calculation table, which Sonia also did for us,
14 that yes, we have now enrolled almost 600
15 unexposed in the comparison group, but you can see that
16 to have 80 percent power, just looking at changes
17 in the overall 2 percent frequency of birth
18 defects, we still need to go further to have 875.
19 And you can see that if you try to get to changes
20 in the frequency of cleft lip and palate, which,
21 of course, the lamotrigine exposure example puts
22 on the table, you really need thousands of

1 enrollees.

2 And so one of my take-home messages for
3 you is pregnancy registries need to be designed to
4 continue until you are able to speak to the
5 frequency of specific malformations, not all
6 malformations. And the only way you are going to
7 do that is if you have funding that continues long
8 enough to have thousands of enrollees. We have
9 now enrolled over 9,000 women, for example.

10 This is our comparison group. At the
11 time, there were 544 recruited. You can see these
12 are the malformations that are listed. If you are
13 one who likes the historical controls, I challenge
14 you to find this listed in any of the lists of
15 abnormalities in those tabulations. Some of these
16 are very common findings in the general population.
17 You can see one of the points here that I haven't
18 talked about but is a major issue, septal defects
19 are found in great frequency in all the imaging
20 that newborns have these days. And you have to
21 decide what size parameters you are going to use.
22 We exclude the muscular VSDs because they are

1 extremely common and most of them go away. And we
2 only include atrial septal defects if they have a
3 certain size measurement. And, obviously, that is
4 something that every registry has to decide
5 separately.

6 Now, who are the women who refer them,
7 and who are the women who enroll as the comparison
8 group? This is a slide Sonia made for me. You
9 can see that she has listed in the middle the
10 women who are taking the seizure medication who
11 refer their friends. And so here are their
12 friends on the left. And the women who referred
13 them are in the middle. And then here is the
14 lamotrigine comparison group on the right side.

15 A pregnancy registry can make no
16 pretense of enrolling a wide spectrum of society.
17 Look here. Post-college education, significant
18 number of these people. The folks who sign up for
19 a pregnancy registry are not a random sample of
20 society, no way to get around that. That is the
21 reality.

22 Likewise, that means that they are not

1 going to be people with significant exposures to
2 things that we know they shouldn't be doing. So
3 for cigarette smoking, very small rate of smoking
4 a pack or more a day. The same is true for
5 alcohol use.

6 But if you bought at the FDA the
7 manufacturer's preference for saying four percent
8 is a normal rate of occurrence of birth defects,
9 look what you would see. For the carbamazepine-
10 exposed pregnancies, which is considered a
11 teratogenic exposure, although of modest severity,
12 that would just ride right under that four
13 percent, would not be detected. Obviously
14 valproate would stand out, but valproate stands
15 out in every analysis you do in anticonvulsant
16 drugs.

17 And here Sonia has shown this. And so
18 you can see that our challenge for the women who
19 are being enrolled who are friends and family
20 members is to get them to enroll earlier. Right
21 now we haven't been stressing that, but we hope
22 among the advocates for this registry, the

1 obstetricians and the neurologists, who are a
2 predominant source of referrals, that we can
3 include in their message to the woman, "Please do
4 it soon, rather than waiting until after you have
5 had any prenatal screening."

6 So, in summary, I think if you are going
7 to have a pregnancy registry, you really need to
8 spend some time talking about what you are going
9 to include and exclude before you get started. You
10 need to have on your team someone who knows what
11 these abnormalities are. We have a pediatrician
12 sitting here. And there are plenty of
13 pediatricians and neonatologists that could be
14 very important contributors to a pregnancy
15 registry, instead of, as I mentioned, the system
16 our research assistants often use. They will
17 Google something because they have no idea what it
18 is. And you don't want that to be the basis for
19 deciding whether something counts or not.

20 You need I think the unexposed
21 comparison group, where you have the same staff,
22 the same interviews, the same process. You are

1 encouraging the woman to sign the form so we could
2 get the copies of the records when the woman says,
3 "We saw the orthopedist last week," that you can
4 get her to help you get the results from the
5 orthopedist's exam, so forth. And then
6 ultimately, of course, you need to have someone as
7 skilled as Sonia who can do the analyses where you
8 subdivide by the women who enroll before they have
9 had prenatal screening versus the women who enroll
10 after that.

11 So, in summary, these are the folks who
12 do all of the work for us and would just emphasize
13 the importance of the FDA considering the
14 possibility of encouraging more vigorously the
15 unexposed comparison group as a component of any
16 registry going forward.

17 Thank you.

18 (Applause.)

19 DR. TASSINARI: Time for some clarifying
20 questions. Any from the panel?

21 DR. SAHIN: Dr. Holmes, could you talk
22 about the governance structure of the North

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

84

1 American Anti-Epileptic Drug Registry, please?

2 DR. HOLMES: Sure. We have been very
3 fortunate in having a scientific advisory
4 committee that has remained very much constant
5 since we began in 1997. And so what we have done,
6 initially meeting twice a year, now once a year,
7 with these folks -- and Jan, to my right, Jan
8 Cragan from CDC, is a member. Two neurologists;
9 an obstetrician; epidemiologist; and a woman from
10 the epilepsy program at NIH constitute the six
11 people. We meet and go over our findings. We are
12 meeting, actually, this coming Monday. We go
13 through the state of the registry, what is
14 happening, what we found. We go through the
15 marketing. We get the answer to Elise's question
16 about how many women signed up this year on the
17 internet versus how many were referred by the
18 obstetrician versus referred by the neurologists
19 and so forth.

20 And then we, particularly in the
21 beginning, presented questions of when do we
22 publish this finding. And initially we referred

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

85

1 to medications by number so that when we discussed
2 them with the scientific advisers, they just knew
3 it as drug number 3, drug number 5, or whatever.
4 And we made the decision to release it. And then
5 they learned that the first drug we released was
6 Phenobarbital. And we asked them to guess what we
7 were releasing. And, of course, they were all
8 over the place but had no idea that it was
9 Phenobarbital. And then the second drug whose
10 findings we released was drug number 5. And that
11 turned out to be valproate. So we have gone
12 through that process early on.

13 Then we had a moment of having to decide
14 what we do with the new drugs where the risk for
15 malformations is more subtle. And that is where
16 the lamotrigine issue came up. And we had the
17 decision to make about whether to release the
18 findings when the first 700 had been enrolled and
19 we had this dramatic increase in the frequency of
20 oral clefts. And the group made the decision that
21 we should go ahead and publish that, and we did.
22 And anybody who is familiar with this literature

1 knows that it has been debated a lot ever since
2 that came out and you saw in Sonia's slide that
3 the rate has dropped steadily. And we predict
4 that it's ultimately once you get up to three or
5 four thousand enrollees, you will get down to a
6 point that is probably going to be higher than the
7 general population rate but not nearly as scary as
8 that initial figure was.

9 So it's been us talking to them, showing
10 them our findings, what do you think, this is what
11 we think we should do. The good news is it has
12 been a steady source of advice, very little
13 turnover in the group. And that has worked. It
14 was particularly important in the early years,
15 when we were debating about when to release
16 something. It is not nearly as much of an issue
17 now. I mean, Sonia showed you a very
18 sophisticated study that she and some of her
19 colleagues at the School of Public Health have
20 done on enrollment. This is the kind of finding
21 that is very sophisticated and very interesting,
22 but it's not something that the scientific

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

87

1 advisory committee is going to agonize about. It's
2 just going to be fascinating to see it documented.
3 But early on, it was, do we release? Do we run the
4 risk of scaring people? Do we wait?

5 And so, you know, for a pregnancy
6 registry with a limited funding, you don't pay
7 these people. We don't pay the women who enroll.
8 And so you're depending on the goodwill of
9 colleagues who are interested in a topic and are
10 willing to come to Boston for a day each -- well,
11 it used to be twice a year, now once a year, to go
12 over the findings. And we are grateful to them
13 for having done that for so long because that has
14 really made it work.

15 You can imagine another model where you
16 would be paying folks thousands of dollars and so
17 forth, but that just is not a realistic part of a
18 pregnancy registry budget. But that is how it has
19 worked. We meet separately and then we end that
20 discussion and decide what we want to discuss with
21 the representatives of the sponsors. And then the
22 sponsors are invited in, their representatives,

1 usually one or occasionally two for each company.

2 And so we and the representatives for the sponsors
3 go over what we think is ready for prime time to
4 talk about.

5 And when we publish something, we send
6 around the manuscript to the sponsors a month
7 before we submit it so they have a chance to give
8 us their comments, questions, whatever with the
9 understanding that we will consider whatever they
10 say, but we necessarily won't change anything
11 based on what they say.

12 And that has been another thing that has
13 evolved since 1997. Initially a lot of the
14 sponsors were very opposed to the idea of separate
15 meetings, where we only met with the scientific
16 advisers, and the people writing the checks were
17 not in the room. But gradually over time, they
18 became more comfortable with that.

19 And now our biggest question is, will
20 the support continue? And we don't have any way
21 to know whether it will or not, but you can see
22 that if you are beginning to talk about specific

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

89

1 malformations, you have got to continue. I mean,
2 a registry stops after 500 enrollees. You're not
3 even to first base. And, you know, that's the big
4 unanswered question. Will the companies feel the
5 importance of continuing so we can begin to talk
6 about heart defects and oral clefts and spina
7 bifida and et cetera because I think that's where
8 these registries should go if the exposure is
9 common enough and the enrollment is at high enough
10 rate?

11 DR. DANA: Hello. It's Adrian Dana. I
12 had a clarifying question about the communication.
13 And, you know, you say you decide to communicate.
14 You know, I think that the communicating negative
15 results in this setting is just as important to
16 exposed women as communicating, you know, positive
17 results of a defect that you are concerned about.
18 And so, you know, what we have done in the past is
19 we just communicate on a periodic basis. You
20 know, if we had something that needed to be
21 communicated more emergently, we would. And so I
22 wondered, do you communicate on a yearly basis? Do

1 you put together some kind of a report or do you
2 only communicate when you have a concern?

3 DR. HOLMES: One of the references in my
4 slides was Sonia was the first author of the paper
5 that appeared in Neurology in 2012. And that was
6 the 11 drugs which had been taken as monotherapy
7 by at least 50 enrolled women. And so among those
8 11, you have 2 or 3 good news stories, reassurance
9 that this drug, that drug was not associated with
10 a significant increase. So we have done both. But
11 we have not had a systematic -- we haven't had a
12 routine.

13 The Australian Anti-Epileptic Drug
14 Pregnancy Registry is one that does what you were
15 asking about. They every year publish wherever
16 they are, what their results are. So the groups
17 have done it different ways.

18 DR. TASSINARI: We will take one more
19 question, and then we will head to break.

20 DR. NGUYEN: Dr. Holmes, do you think
21 that your friends and family strategy for a
22 comparator group is generalizable to other

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

91

1 products, like vaccines?

2 DR. HOLMES: I think it is the sort of
3 thing that people need to look at and think about.
4 For us, it has worked. And I think the value of
5 an internal comparison group is really powerful.
6 And so it would be interesting to hear the people
7 who have worked on vaccines to comment on that.

8 But you need to get away from the idea
9 that -- using historical comparison groups and get
10 your own comparison group so you've got your own
11 things that happen to real people, real time. So
12 that's my plus side, but I would be interested to
13 know what they think about using it.

14 DR. TASSINARI: Well, thank you. We
15 have reached our break time. Okay. Go ahead.

16 MS. MOYERS: Just one housekeeping
17 announcement for the invited panelists who let us
18 know they would like to participate in the buffet
19 lunch. If you could just please pay at the kiosk?
20 If you have any questions, Paul Tran is at the
21 registration desk. That is for the invited
22 panelists. Thank you.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

92

1 DR. TASSINARI: We will resume at 10:00
2 o'clock.

3 (Off the record.)

4 (On the record.)

5 DR. TASSINARI: Well, I think we will
6 begin with our next presentation. We have two
7 more presentations this morning. And then we have
8 set aside some time to address a few questions
9 that we have for the panelists related to the
10 information that we have been listening to this
11 morning.

12 So, with that, I'd like to ask Dr.
13 Albano, how is from INC Research, to present on
14 multi-product registries. Thank you.

15 MULTI-PRODUCT REGISTRIES

16 DR. ALBANO: Good morning. I am pleased
17 to have the opportunity to speak to you all today
18 and to share some of our experience with multi-
19 product registries.

20 I wanted to begin by just reviewing a
21 few of the important points that have already been
22 brought up this morning: first, that most

1 information on the safety or risk of drugs related
2 to pregnancy is collected after the drug has been
3 approved and is used in pregnant women in the
4 real-world setting. Pregnancy registries are
5 generally implemented when there is either a
6 safety concern, an indication for use during
7 pregnancy, or a high likelihood of use in women of
8 reproductive age. The purpose of pregnancy
9 exposure registries is to provide human data on
10 the safety risk profile of pharmaceutical products
11 during pregnancy. In order to fulfill the goal of
12 informing the decisions of patients and health
13 care providers, it is imperative to initiate the
14 registry as soon as possible using the most
15 effective design strategy.

16 The objectives of this presentation are
17 to differentiate single versus multi-product or
18 disease-based registries; to demonstrate the
19 appropriate use of each with examples; to discuss
20 advantages, challenges, and special
21 considerations; and to delineate some of the
22 perceived barriers to implementation. The first

1 distinction to be made is between a product and a
2 disease registry. In a product registry, the
3 eligible population is identified based on
4 exposure to a particular drug, biologic, or
5 medical device, although the latter is of less
6 relevance with regard to pregnancy registries. In
7 a disease registry, the eligible population is
8 identified by a common condition or diagnosis.
9 Individuals may be treated or untreated. And
10 among those treated, their therapy may include one
11 or several different drug products. So while the
12 product and disease registries have some distinct
13 methodological differences, both have the
14 potential to result in either a single or a multi-
15 product registry. We will be discussing them
16 together in the overall framework of multi-product
17 registries.

18 As the term implies, a single product
19 registry monitors a single drug or biologic
20 product. There may be multiple formulations,
21 varying doses, or different routes of
22 administration as well as both brand and unbranded

1 versions. Single product registries are most
2 appropriate for newly approved products, the first
3 product in a new drug class, when there is a new
4 indication for a marketed product, when there is a
5 high likelihood for use in pregnant women of
6 reproductive age, when the product is approved for
7 use in a unique population, when the product has a
8 known pregnancy or fetal risk, and when there is
9 excess risk for a product compared to other
10 treatment options.

11 As an example of a registry for a
12 product with a known safety risk, the Ribavirin
13 Pregnancy Registry monitors fetal exposures to
14 brand and generic versions of products with a
15 ribavirin component that are marketed in the
16 United States. In contrast, the Adenovirus Vaccine
17 Pregnancy Registry was designed to monitor
18 outcomes of fetal exposure to adenovirus vaccine
19 in the U.S. military, a unique population with a
20 large number of reproductive age women.

21 In a simple scenario, a multi-product
22 registry monitors multiple different products for

1 the same indication from a single pharmaceutical
2 company. This type of registry is appropriate
3 when the products are within a single drug class,
4 have a similar risk profile, or are likely to be
5 used in the same patient population. This type of
6 registry may also be appropriate when concomitant
7 exposures are of concern or when a combined
8 registry is operationally and logistically
9 feasible.

10 Each of these registries monitors
11 pregnancy's exposures to multiple drugs used to
12 treat the same condition or disease. The
13 Sumatriptan, Naratriptan, and Treximet Pregnancy
14 Registry includes three drugs indicated for the
15 treatment of migraines. The MoTHER Pregnancy
16 Registry has expanded to include three HER2+
17 breast cancer treatments.

18 In the complex scenario, multi-product
19 or disease-based registries monitor all of the
20 marketed products used to treat a particular
21 disease in a given region. This type of registry
22 is appropriate when the products are manufactured

1 in combination, there are complex multi-drug
2 treatment regimens, there is a high likelihood of
3 polytherapy, there are frequent and new product
4 approvals, internal comparisons are desirable, or
5 when confounding disease or population
6 characteristics may exist.

7 Two examples of long-term registries are
8 the North American Anti-Epileptic Drug Pregnancy
9 Registry and the Antiviral Pregnancy Registry. You
10 have already heard quite a bit about the North
11 American Registry, which monitors approximately 38
12 drug products used individually as monotherapy or
13 as complementary polytherapy. The APR monitors
14 approximately 30 single drug and 8 combination
15 drug products. Twenty-five are indicated for HIV.
16 Two are indicated for both HIV and hepatitis B.
17 And three are indicated for hepatitis B alone.

18 I'm going to go into a few of the
19 results from the Antiretroviral Pregnancy
20 Registry. The registry began as a single drug
21 registry in 1989 and has expanded over the past
22 nearly 25 years to become a multi-product, multi-

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

98

1 sponsor registry. Through July of 2013, there
2 have been almost 18,500 prospective cases enrolled
3 from 67 countries. Seventy-eight percent of the
4 reports in the registry are from the U.S. and its
5 territories, and 9 and a half percent of
6 enrollments have been lost to follow-up. Among
7 the 38 drugs being monitored, there are currently
8 23 participating manufacturers.

9 Through July of 2013, there have been
10 more than 16,300 prospective reports with outcome.
11 Approximately half, or 48 percent, of pregnancies
12 have exposure in the first trimester. Thirty-nine
13 percent were initially exposed in the second
14 trimester. And 13 percent were exposed beginning
15 in the third trimester.

16 Among the 16,589 outcomes, there were
17 15,451 live births and 445 defect cases. The
18 overall prevalence of birth defects was 2.9
19 percent. The 95 percent confidence interval
20 ranges from 2.6 to 3.2 percent. The APR uses a
21 comparison group primarily of the MACDP, which
22 from 1989 to 2003 has a birth defect prevalence of

1 2.72 percent.

2 Among first trimester exposures, the
3 prevalence of birth defects was 2.9 with a 95
4 percent confidence interval from 2.5 to 3.3
5 percent. This is compared internally by later
6 trimesters, in the second and third trimester, but
7 the risk of defects is not significant. The risk
8 is 1.02.

9 In addition to evaluating drugs in
10 aggregate and by class of antiretroviral therapy,
11 they are analyzed individually when sufficient
12 numbers of exposures have accumulated to warrant a
13 separate analysis. The APR uses a threshold of
14 200 first trimester exposed cases. To date, there
15 has been no concern among the individual drugs
16 analyzed with the exception of two drugs,
17 nelfinavir and didanosine, which have a modest but
18 statistically significant elevated risk overall
19 compared to the MACDP. However, there is no
20 discernible pattern among the specific defects
21 that had been reported.

22 Our Advisory Committee reviews in

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

100

1 aggregate and individual cases on a semiannual
2 basis and as part of our published annual and
3 semiannual reports provides a consensus statement
4 that is there, a cumulative and comprehensive
5 review of the data. I will summarize it by saying
6 that the Antiretroviral Pregnancy Registry finds
7 no apparent increase in the frequency of specific
8 defects with first trimester exposures and no
9 pattern to suggest a common cause. However,
10 potential limitations of registries should be
11 recognized.

12 The APR is funded by pharmaceutical
13 companies listed here. And the APR always wants
14 to acknowledge the outstanding efforts of the
15 clinicians who submit cases as well as the
16 valuable contributions of our Steering Committee.
17 And we'll get into the governance structure of the
18 Steering Committee a little later on.

19 I'm going to talk about some of the
20 advantages and challenges of the complex multi-
21 drug registries. So, despite their complexity,
22 multi-product or disease-based registries have

1 distinct advantages over single product
2 registries. They are logical in that they avoid
3 duplicate efforts in the establishment of the
4 registry, but also from a reporting perspective
5 for health care providers, pharmaceutical
6 companies, and regulators. They are economical,
7 pooling resources and budgets from multiple
8 stakeholders. Not only are multi-product
9 registries more efficient with their use of
10 limited budgets and resource but with their
11 utilization of experts in the roles of Advisory
12 Board members and birth defect evaluators.

13 I will touch more on analytical
14 considerations later, but multi-product registries
15 are methodologically advantageous to the
16 standardization of data collection, case
17 evaluation, and statistical analysis, not to
18 mention enhanced validity and power.

19 Multi-product registries reduce
20 competition for eligible patients and streamline
21 health care provider participation. They also
22 offer a more robust consolidated awareness effort.

1 The most important advantages, however, are from
2 the clinical point of view. Multi-product
3 registries serve as a centralized resource for
4 patients and physicians. They minimize the
5 reporting burden of health care providers,
6 increase incentive to participate for providing a
7 single comprehensive reporting mechanism. They
8 offer a coherent assessment of the available data.
9 And they provide a consistent message of the
10 current understanding regarding risk.

11 Despite the many advantages, there are
12 several challenges. I call these the C's of
13 multi-product registries. First is complexity.
14 They are operationally and analytically complex
15 and require a high degree of expertise to
16 implement.

17 Collaboration. They require agreement
18 from companies competing in the same therapeutic
19 area to work together, adopt common processes,
20 adhere to policies and timelines.

21 Communication. All parties must respect
22 the established lines of communication, which

1 should be appropriately documented.

2 Competition. Innovator companies,
3 being the first at the table, are frequently
4 responsible for the setup and implementation of
5 such a registry.

6 Confidentiality. It is necessary to
7 have sensitivity to the proprietary aspects of
8 drug discovery, marketing, and lifecycle
9 management as well as direct communications
10 between regulatory agencies and pharmaceutical
11 companies that may occur outside of the context of
12 the registry but which may have relevance to the
13 registry itself.

14 And commitment. Various stakeholders
15 may not have the same level of commitment
16 regarding their participation.

17 Analyses of multi-product registries can
18 be multi-tiered. They can be at the individual
19 drug class level, they can compare monotherapy
20 versus polytherapy, or they can look at the
21 overall registry experience for all the drugs
22 being monitored. We have had an in-depth review

1 already of comparison groups and potential
2 confounders. So we'll move past those topics.

3 In regard to special considerations, as
4 a mentor of mine likes to say, failing to plan is
5 planning to fail. And that is certainly the case
6 when it comes to registries. They require unique
7 approaches in the design, data collection,
8 statistical analysis, reporting, and the
9 dissemination of data.

10 An imperative to the success of any
11 complex collaborative registry is to have a well-
12 defined governance structure. By "collaborative
13 registry," I am referring to one in which multiple
14 stakeholders work together to meet one or more
15 specific objectives, whether this is by choice or
16 by mandate.

17 This figure depicts the governance
18 structure of the Antiretroviral Pregnancy
19 Registry, which is overseen by a steering
20 committee comprised of three groups. The
21 Scientific Advisory Board is made up of experts in
22 the appropriate fields from academia, government,

1 and private practice. The advisors provide
2 scientific oversight as well as review and
3 interpret the data. The sponsor representatives
4 from the pharmaceutical industry oversee the
5 registry management, budget approvals, and
6 regulatory reporting. The Registry Coordinating
7 Center is responsible for the managing daily
8 operations from enrollment to data collection,
9 statistically analysis, report writing,
10 interactions with the IRB, and facilitating the
11 interaction of both the advisors and the sponsors.
12 The primary benefit of such a governance structure
13 is the clear separation of scientific, financial,
14 and operational activities.

15 When planning research, it is vital to
16 consider both the business and the scientific
17 objectives and to find a balance. Business
18 objectives address marketing, treatment options,
19 satisfying post-approval regulatory commitments,
20 or product differentiation while scientific
21 objectives address product effectiveness and
22 safety, cost versus benefits, patient/physician

1 satisfaction, utilization patterns, and patient
2 adherence. Without sensitivity to the business
3 objectives, which often drive funding sources, the
4 scientific objectives may not be realized.

5 In order to alleviate some of the
6 uncertainty with regard to preferred methodologies
7 and design strategies, it would be helpful to have
8 the following updated regulatory guidance that
9 specifically addresses best practices, gives
10 directives, unacceptable recruitment methods, and
11 encourages consistency across therapeutic areas.

12 In conclusion, the implementation of an
13 effective pregnancy registry hinges on identifying
14 the most appropriate design. Expert consultation
15 is a critical step in understanding the regulatory
16 landscape and drug or population-specific nuances.
17 Engaging stakeholders to gain broad participation
18 and planning early to ensure the greatest utility
19 is realized.

20 Thank you.

21 (Applause.)

22 DR. TASSINARI: Clarifying questions

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

107

1 from the panel?

2 DR. IYASU: Well, thank you very much.
3 That was a very nice presentation. It's great how
4 you discussed sort of the governance structure,
5 which is a very important element in terms of
6 success of such registries. Could you speak to
7 the issues of the trade-offs between product-
8 specific analysis versus sort of the aggregate
9 because, you know, there are multiple
10 pharmaceutical companies involved here? So how is
11 that achieved, actually, in terms of data sharing
12 about information about product-specific issues?

13 DR. ALBANO: The way the APR conducts
14 its analysis, INC Research serving as the
15 coordinating center for the registry, it is
16 responsible for collecting all the data. They
17 hold the data. And they analyze the data and
18 distribute it in aggregate to the participating
19 manufacturers and the advisory committee who
20 reviews the data semiannually. So we have a
21 threshold that has to be met before we do product-
22 specific analyses. And those are all done as per

1 the routine analysis that is already planned out
2 for the registry and reported as such. So
3 everyone has accessibility to all the products. We
4 do, you know, hold that threshold until we get a
5 sufficient number of exposures before we conduct
6 that.

7 DR. TASSINARI: I'd like to introduce
8 Dr. Adel Abou-Ali, who is our industry
9 representative. And he is going to speak on data
10 collection and experiences with vaccines.

11 DR. ABOU-ALI: Thank you very much.

12 DATA COLLECTION/EXPERIENCE WITH
13 VACCINES

14 DR. ABOU-ALI: As a start, I would like
15 to thank the FDA for inviting a representative
16 from the vaccine industry for such an important
17 event. This is my first presentation on this
18 particular topic after moving from government to
19 the industry. And I will present another similar
20 topic at the WHO in Geneva next month. And I have
21 to admit putting those slides together was really
22 challenging, even though in the drug arena, there

1 is a lot and plenty of information available on
2 drug exposure pregnancy registries, but for the
3 vaccine industry, the picture is slightly
4 different. So it was kind of challenging to put
5 those slides together on the data collection and
6 experience with the vaccine.

7 Quick background. As Dr. Iyasu and Dr.
8 Sahin, Dr. Diaz referred in their backgrounds, the
9 importance for pregnancy registry in the vaccine
10 industry is very similar to drug
11 registry/pregnancy registry. The preclinical data
12 and the premarketing safety evaluation do not
13 provide enough information about the safety for
14 vaccines, very similar to what is happening in the
15 drug arena.

16 In addition to that, there is a
17 theoretical risk of fetal transmission in some
18 kind of particular vaccines, specifically for
19 those vaccines like MMR and varicella, that might
20 cause a risk by transmission to the fetus. Also,
21 recent recommendations recommend giving the
22 influenza vaccines and Tdap vaccines to all

1 pregnant women. So having information about dose
2 exposures is of particular importance.

3 In order to give a quick picture about
4 how it is within the vaccine industry, I found a
5 report that was prepared in a similar meeting at
6 the EMA, European Medical Agency, about the
7 overview of pregnancy exposure registries, very
8 helpful to describe how it is in the vaccine
9 industry. They referred to the sources of
10 pregnancy registries according to who said
11 pregnancy into certain classifications. This
12 classification includes that pharmaceutical
13 companies may be responsible for pregnancy
14 exposure registries. It could come from academic
15 groups. It could come from research groups. And
16 there are other new and alternative sources, such
17 as the health care databases, like the CPRD, and
18 the population-based surveillance registers, such
19 as in Northern countries or Scandinavian
20 countries.

21 Pregnancy exposure registries can also
22 be classified according to the exposure. It could

1 be a single drug registry or a drug class registry
2 or a disease registry. In the vaccine industry,
3 the most common one is the single drug registry.
4 In my limited exposure so far in the vaccine
5 industry, I didn't see any multiple drug
6 registries or drug class registries. It's all
7 with a single drug registry.

8 It also can be classified according to
9 the location and to country-specific and
10 international. So far the most common is the
11 country-specific registries. But I can see that
12 we're moving slowly toward the global registries.
13 We just started the new global registry for the
14 flu vaccine QIV. It is going to be here in the
15 United States as well as in Europe. And I think
16 other companies are taking the same approach
17 slowly.

18 In establishing the registries, the
19 vaccine company depends basically on guidance from
20 regulatory agencies. Here in the United States,
21 one of the guidance for industry is one of the
22 important guidances that we are using to establish

1 our vaccine registries, in addition to the
2 reviewer guidance that came in 2005. Both of them
3 provide very useful information about how to
4 establish the registry. And I'm going to use the
5 elements that were explained in the guidance that
6 was published in 2002 from the FDA to try to walk
7 you through how we establish our pregnancy
8 registries in the vaccine arena.

9 The European Medical Agency came out
10 with similar guidance in 2005 and described the
11 process in a very similar way. So these
12 guidelines provided six very important elements
13 that we use on a regular basis when we are trying
14 to establish our registries, starting from the
15 design to equipment, the reporting sources,
16 explaining how to collect the data, and how to
17 make the follow-up, how to conduct data analysis,
18 and how to report the results.

19 Starting with the design, as Dr. Holmes
20 referred in the beginning, pregnancy registries
21 are observational and not interventional. It's
22 noninterventional. It's either active

1 surveillance or passive surveillance according to
2 the description in the FDA guidelines. In the
3 drug arena, the most common form is the active
4 surveillance or the cohort even monitoring
5 registries. In vaccines so far, what I have seen
6 in the industry of vaccines, it is mostly passive
7 surveillance observational studies. It could be
8 prospective or retrospective. And, ideally, it
9 should be prospective to avoid some kinds of
10 biases. Prospectively means that you start
11 enrollment prior to pregnancy or early during that
12 pregnancy. And we're going to explain this in
13 details.

14 So in general vaccine registry, we use
15 passive surveillance. And this passive
16 surveillance is basically the women on voluntary
17 participation. It's dependent on spontaneous
18 reporting.

19 It's a HIPAA-compliant system for most
20 companies, including Sanofi Pasteur. And it
21 mainly aims to collect data and information on the
22 vaccine exposure and the pregnancy outcome in

1 order to monitor for any potential safety signals.
2 So it's a mean for signal detection in other ways
3 or in other words.

4 The enrollment in those registries is
5 usually, as explained earlier, prospectively or
6 retrospectively. So when we receive the cases or
7 when the registry is being defined after the
8 exposure of the vaccine but before the conduct of
9 any prenatal tests or knowing what is the outcome
10 of the pregnancy, we consider this prospective.
11 Retrospectively, on the other hand, is when the
12 registry is notified after the outcome of the
13 pregnancy is already known. And usually this
14 happened from the patient, not from the health
15 care provider.

16 The second element in the guidelines
17 that we use in our vaccine registries is the
18 recruitment. The guidelines described how
19 companies can do recruitment and announcement. And
20 I find in vaccine, in particular, the most
21 important way of announcement or recruitment is
22 through labeling. Usually the package inserts

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

115

1 contain the phone number or a web address for
2 patients and health care providers to how to
3 report any cases.

4 The second most common way of
5 announcement or recruitment for patients is the
6 company websites. So far, most of the
7 pharmaceutical companies have websites for their
8 pregnancy registries. Sanofi Pasteur has
9 sanofipasteurpregnancyregistry.com. GSK has a
10 very similar one. Merck has a similar one. All
11 of them have those websites. On the website,
12 usually there is a description of the different
13 pregnancy registries that is taking place,
14 including both drug and vaccines and the mean of
15 communications to report cases for those
16 registries.

17 Other means include professional
18 journals; professional and maternal/infant
19 advocacy group newsletters; informational booths
20 at professional meetings; and, finally, lectures
21 and talks, such as this public meeting. So I'm
22 going to show you later on our website and our

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

116

1 phone number, a toll-free phone number, where you
2 can report cases. So patient or health care
3 providers can use those means to report cases for
4 the pregnancy registry.

5 The third element is the reporting
6 sources. Usually the most common reporting source
7 is the health care provider. Followed by the
8 health care provider is the pregnant women
9 themselves, who are exposed to the vaccines.

10 The reports can be made either by a
11 toll-free number, as explained earlier, or from a
12 website. Each company has one toll-free number
13 that is for all of their vaccine pregnancies. And
14 through this phone number, you can report any
15 cases.

16 In addition to those reports that come
17 from health care providers and consumers, there
18 are other ways that we can collect data on
19 exposure to vaccine during pregnancy. Such
20 sources or means include company-sponsored
21 studies. So, as you see, this is a description of
22 the best surveillance practices we conduct at our

1 company. On the other hand, there are other
2 studies that can be taking place besides this
3 specific surveillance. Any cases on those studies
4 can result in reports that go into the registry.

5 In addition to those company-sponsored
6 studies, there is the medical literature and cases
7 being reported to health authorities, such as the
8 FDA.

9 The fourth element is the data
10 collection and the follow-up. Usually the
11 pregnancy cases, with or without adverse events,
12 are being recorded in the company. Any cases that
13 are reported to the company are being kept in a
14 global pharmacovigilance database and are reviewed
15 frequently by product safety officers, which in
16 general are clinicians that reviewed those cases.

17 The pregnancy outcomes are followed up
18 via questionnaire. This questionnaire is sent to
19 a reporter, whether it is a health care provider
20 or a patient, and collects information about
21 different data. And this usually happens several
22 times during the pregnancy and up to three times

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

118

1 following the outcome itself. So if there was a
2 child as an outcome, we follow up for up to three
3 times if we didn't receive any information that
4 said, "We closed the case." Information collected
5 in this questionnaire or in this pregnancy form
6 would include information about the demographic
7 data, include information about the vaccine
8 itself, the product, the brand, and administration
9 date. It also can include details about the
10 pregnancy, like the gestational age, date of last
11 menstrual period, and other information.

12 When it comes to reporting the pregnancy
13 outcomes, it depends on the type of the outcome.
14 So if the outcome for certain criteria to be
15 considered, severe adverse event, which may
16 include the spontaneous abortion, stillbirth,
17 congenital anomalies, according to the Title 21 of
18 the Code of Federal Regulations, we have to report
19 those within 15 days besides having them in our
20 global database.

21 If the outcome does not fulfill this,
22 usually the event being kept in our global

1 database and reported to a regulatory agency
2 through the periodic safety update reporting
3 systems, which is different from one agency to
4 another. And those kinds of evidence include all
5 other cases of pregnancy, that do not meet any
6 definition of seriousness and that also include
7 all of the serious adverse events that were
8 reported earlier within 15 days.

9 The last element of the guidelines that
10 we usually follow when we establish our pregnancy
11 registries is the data analysis. We usually
12 analyze the data being collected prospectively and
13 retrospectively separated from each other. For
14 the prospectively collected data, we usually
15 certify them according to the pregnancy outcomes.
16 So we would classify by spontaneous abortion,
17 elective termination, fetal death or stillbirth.
18 We classify by live birth, also congenital
19 anomalies.

20 If the information or the data is
21 collected retrospectively, we only consider it for
22 qualitative evaluation. We do not consider it for

1 quantitative evaluation. Each of those cases
2 reported either prospectively or retrospectively
3 is evaluated for the time of exposure, the time of
4 conception, the maternal age, the medical history,
5 also for biological plausibility, and any drugs
6 that have been taken besides the vaccine during
7 the pregnancy phase.

8 From the analysis, we can get occurrence
9 rates and calculate them. And from those
10 occurrence rates, we actually can find out if
11 there is some potential signal or not. And if
12 there is a potential signal, we can act
13 accordingly.

14 The challenges and limitations we face
15 in the vaccine industry so far are not so
16 different from what drug exposure pregnancy
17 registry is facing. We face the same limitation
18 of completeness of data. Usually we do not have
19 enough information from the data collected,
20 especially if the reporter is a patient, not a
21 health care provider. There is a lot of missing
22 data on the branding. And to be more specific,

1 there is also missing medical confirmation,
2 specifically if it was provided from the patient,
3 not from the health care provider. We also face
4 challenges with loss to follow-up. If the health
5 care provider has contact with the women after the
6 outcome takes place, then he would have a follow-
7 up, but if not, then there is no way to have a
8 follow-up on such cases. We also face a challenge
9 with lack of precise denominators since this is
10 basically a passive surveillance system, which is
11 basically dependent on spontaneous reporting. We
12 do not have usually a precise denominator, which
13 affects the calculation later on. We also face
14 challenges with the control and unexposed group.

15 Walking through an example from
16 Sanofi

17 Pasteur pregnancy registries to
18 highlight what I have explained earlier, Sanofi
19 Pasteur so far has four active pregnancy
20 registries: one for Menactra, Adacel, Fluzone,
21 and Fluzone QIV. And Fluzone QIV, it's a global
22 pregnancy registry that we just started. So it's

1 kind of an educational experience for us to
2 explore how to do this thing globally, which will
3 include a totally different set of challenges and
4 limitations.

5 An example of the Adacel, for example,
6 to explain the limitations we are facing, in a
7 period of six years, from June 2005 until June
8 2011, we received 577 pregnancy reports. Ninety-
9 two percent of those reports were spontaneous
10 reports, which is the 528. And 49 study reports,
11 which is about 8 percent of the reports, came from
12 other studies. Out of the 528, we had 345 lost to
13 follow-up, which is about 67 percent of the
14 pregnancy. So this can give you an idea about how
15 limited this process is and the challenge we're
16 facing in this. This is not in particular to
17 Sanofi Pasteur vaccine registries, but it can
18 apply to other registries as well for other
19 companies.

20 In summary, in the vaccine area, the
21 pregnancy registry is a mean for signal detection.
22 It does not answer the question, but it can help

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

123

1 you identify those potential signals that need
2 more investigations and more studies. In other
3 ways, vaccine registry can act as hypothesis-
4 generating studies by detecting adverse pregnancy
5 outcomes that may warrant further investigation.
6 Having said that, despite the current limitation
7 of vaccine pregnancy registries, it remains an
8 important source for information.

9 Thank you.

10 (Applause.)

11 DR. TASSINARI: Questions? Comments?

12 Yes, Mike?

13 CLARIFYING QUESTIONS FOR THE
14 PRESENTERS

15 FROM THE PANEL

16 DR. GREENE: For the post-marketing
17 surveillance studies that are not required as part
18 of the approval of the drug, what expectation or
19 requirement is there for the registries to report
20 their data to the FDA or does the FDA find out
21 about it by reading about it in the newspaper?

22 DR. NGUYEN: For the ones that are not

1 PMCs and PMRs if this is what you're asking,
2 occasionally we get courtesy copies of
3 information. And in other ways, we do detect it
4 through our routine surveillance of the
5 literature.

6 Additionally, we also have the advantage
7 of our partnering very closely with CDC in the
8 Immunization Safety Office. And together we often
9 monitor the literature that way.

10 DR. YAO: I can also speak to the points
11 that were brought up that there are other separate
12 reporting systems for the requirements to report
13 adverse events, et cetera, et cetera. And
14 sometimes in that context, we will find out this
15 is how they were obtained. But it's not, as you
16 point out, a requirement if we didn't ask them or
17 tell them to do it.

18 I think in most cases, companies when
19 they are interested in trying to do something like
20 this will actually, you know, come to FDA and talk
21 to that, "What would be the way to best do it? How
22 would you like to report it?" Then there is some

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

125

1 collaboration there often.

2 DR. TASSINARI: I wondered if you could
3 expand a little bit about the challenges you are
4 facing maybe in planning for moving to the global
registry,
5 as you alluded to.

6 DR. ABOU-ALI: Well, as I mentioned,
7 this is new experience for us. And we're moving
8 slowly into it, but we are considering some
9 nontraditional ways of doing that. The first is
10 going to be in Mexico, for example. And we're
11 thinking of using a web-based system to collect
12 the information and establish a pregnancy
13 registry.

14 So, instead of using a paper-based
15 method sending that questionnaire to the health
16 care provider or to the patient and then collect
17 the data back, the health care provider, all the
18 patient can report through an online web-based
19 system application, that that's found online.
20 Other ways is to use Smartphone applications, for
21 example. And we're thinking seriously about doing
22 this with the QIV, Fluzone QIV. Most of the

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

126

1 people right now have Smartphones. And everybody
2 is using it for regular activities. So if you
3 have an application that you can report the
4 adverse events through, this can facilitate the
5 process and increase the enrollment rate as well.

6 So those are some kinds of alternative
7 methods that we're going to be using. Of course,
8 there is a lot challenging or challenges to do
9 that, but we are trying to overcome those.

10 DR. TASSINARI: So, I mean, those sound
11 like approaches that one could take, whether you
12 chose to be within the United States or global or
13 not. I think they're great thoughts in terms of
14 meeting some of the challenges we have.

15 I guess I am still trying to understand
16 what it is that makes it so much more challenging.
17 If you could elaborate a little bit more on why?
18 Why wouldn't you move to a global setting?

19 DR. ABOU-ALI: Why would we move to a
20 global setting, rather than --

21 DR. TASSINARI: Well, I got why would
22 you move to a global setting, but what are you

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

127

1 anticipating that makes it more challenging than
2 just setting up a registry within the United
3 States?

4 DR. ABOU-ALI: Well, definitely you will
5 have a larger sample size probably if we're moving
6 globally, not just locally. This is one of the
7 things. You are increasing your sample size. So
8 we hope that doing a global registry will do that.

9 Other things, lately we have been facing
10 challenges with other regulatory agencies when
11 they approve the product. If the trial is being
12 conducted in the United States, for example, and
13 not in South America, they think that the drug
14 might have different effects, especially with
15 regard to the safety. So if you apply the same
16 concept on pregnancy registry, the same thing. So
17 they would require something locally there.

18 So from a resources point of view, it is
19 easier for us to have this pregnancy registry
20 globally, rather than having multiple local ones.
21 So that's another thing that we're thinking of.

22 DR. DANA: Again, Adrian Dana from

1 Merck. Maybe I can answer some of the challenges
2 that we have faced with at least maybe not global
3 but multinational registries.

4 One of the things that is very difficult
5 is the differing privacy regulations. So, for
6 instance, we have had registries in Canada. Canada
7 is very difficult because we are not allowed to go
8 back to the patient or the provider to get the
9 follow-up data, which is absolutely critical. We
10 have to go back at the time that we, you know,
11 expect delivery to have occurred to find out the
12 data. So that has been extremely limiting for us.

13 So I think one of the major challenges
14 is differing privacy regulations among different
15 areas. Another challenge, of course, is that, you
16 know, up to now, you know, finding this control
17 group is like the holy grail, you know. And so up
18 to now, we have largely been using, you know,
19 basically epidemiologic data from that population.
20 So when you start to get into other regions of the
21 world, you know, the background rates of various
22 adverse events in pregnancy may be differing. And

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

129

1 so we have to find a proper comparison group. And
2 I think those are two of our major challenges.

3 DR. TASSINARI: I actually think that --
4 okay. Michael? Sorry.

5 DR. GREENE: Just as a practical matter,
6 in a scientific advisory committee that I sit on,
7 some of the international reports that come in
8 report complications of pregnancy and/or birth
9 defects in their native language, for which there
10 is no direct translation into English. So that
11 sometimes I will look at a report and it will be
12 translated into English, but it doesn't mean
13 anything in terms of any of the categories of
14 disease that we understand. So it's harder.

15 DR. NGUYEN: I just wanted to follow up
16 the question on your implementation of web-based
17 protocols and Smartphone applications. Have you
18 found in the early experience or in maybe pilot
19 programs that it has helped address the 67 percent
20 loss to follow-up or is it only to improve
21 enrollment?

22 DR. ABOU-ALI: Well, it's only going to

1 be only to improve it. So probably we're going to
2 have some loss. I'm not sure how big it is going
3 to be. But there is only one published study that
4 came from, if I recall, Malaysia. That is where
5 they had a pilot study on a vaccine surveillance
6 through mobile devices. The loss rate was about
7 70 percent as well. So it's about the 67 percent
8 of what we're facing here. But considering that
9 this is going to be an easier way for patient and
10 physician and current time to report, I think it
11 deserved to be explored.

12 TOPIC 1 PANEL DISCUSSION AND Q&A

13 DR. TASSINARI: Well, then I think what
14 we shall do is move into our discussion session.
15 We have three questions. They really are focused,
16 as was this first topic this morning, around the
17 pregnancy exposure registry. If we could have the
18 first question? What we would like to do is
19 canvass your thoughts and, you know, of all kinds
20 and have a discussion a little bit about these
21 exposure registries and specifically what the
22 advantages have been from our experiences and what

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

131

1 the challenges are. And I think we have begun to
2 hear a few of those, in fact.

3 The second question, just to anticipate
4 things, is, how can we fix some of those
5 challenges? But if we can focus a few minutes on
6 what they are and what our experiences have been
7 on the pregnancy exposure registry itself will
8 then flow into, I hope, some thoughtful
9 suggestions for solutions.

10 So I will open this up. I don't know if
11 anybody would like to do this.

12 And, Vicki, you have something?

13 MS. MOYER: Just a reminder if you
14 could please state your name before you speak for
15 the benefit of the transcriptionist as well as the
16 folks who are joining via webcast who can't see us
17 all. Thank you.

18 DR. CHAMBERS: This is Tina Chambers. I
19 had a question related to the prospective nature
20 of pregnancy registries. And maybe this is
21 something that Michael Greene or Lew can answer. I
22 wonder whether you have seen over time or going

1 forward that the sort of definition of prospective
2 is a moving target as prenatal diagnosis moves
3 earlier and earlier in pregnancy and even pre-
4 implantation diagnosis is taking place. And do
5 you see this having an impact on, you know, what
6 actually qualifies as prospective?

7 DR. HOLMES: Let me just tell you what
8 we are seeing in the North American AED Pregnancy
9 Registry. If you go across the United States,
10 there are enormous -- and Mike knows more about
11 this than I do -- variations in obstetrical care.
12 And it's the old East Coast-West Coast. You tend
13 to have the newer technologies more likely to be
14 occurring there or, say, in the center of the
15 country, in the Chicago-Ann Arbor area. And they
16 have larger areas of the country that are using
17 the old systems. And there's a slower process in
18 moving to cell-free fetal DNA and that sort of
19 thing.

20 But Sonia's analysis emphasizes the fact
21 that we have to really be careful in our
22 interviewing to be sure when a woman is enrolled

1 as a pure prospective enrollee, that that really
2 is the case.

3 So you are absolutely right. It is
4 changing. And there are occasionally birth
5 defects now picked up at 10, 11, 12 weeks. So
6 since we started in 1997, there has been a
7 dramatic change. Yes.

8 DR. GREENE: So Lew's example of
9 prospectively ascertained hydronephrosis is a good
10 example because it is easy, relatively easy, by
11 ultrasound to determine tissue-fluid interfaces
12 and something like hydronephrosis jumps right off
13 the screen at the sonographer. But that's not
14 until relatively late in pregnancy. So if a woman
15 had an ultrasound examination at nine weeks when
16 you can't see fetal kidneys and it was normal but
17 later you discover that there is hydronephrosis
18 during pregnancy and then maybe even later, during
19 the pediatric period, it's dismissed as not really
20 being an issue, was that truly a prospective case
21 because she had an ultrasound at nine weeks with
22 respect to hydronephrosis?

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

134

1 You are right. It is a moving target,
2 not only in technology as technology evolves but
3 also as the embryo changes and fetus changes in
4 terms of the diagnosability of birth defects.

5 DR. HOLMES: Melissa, I have another
6 question to put on the table which is an issue for
7 us and I would suspect it is for most pregnancy
8 registries. And it relates to this issue that was
9 referred to with regard to the privacy issues in
10 Canada. About a third of our enrollees are
11 unwilling to sign the forms to obtain copies of
12 the pediatric records on their infants. And I
13 don't get to talk to very many of them, but when
14 someone does get to talk to her about why she
15 doesn't want to do it, unfortunately, the reasons
16 are rather diffuse. And they're usually based on
17 fear that somehow this information is somehow
18 going to be to the detriment of their child. And
19 we can't really very effectively debate that with
20 her.

21 So that's a reality of a pregnancy
22 registry. And so when we publish our results, we

1 divide the results between those where we have the
2 pediatric records to confirm what she has reported
3 and those where we don't. And usually they are
4 similar so that we are not concerned that we're
5 missing a lot of major problems. But if you're
6 working from the statistical standpoint, you are
7 cutting your sample size by a third because, you
8 know, you are already down to the pure prospective
9 enrollees. You're down to the ones that let you
10 get records. And it just keeps cutting your
11 sample size more and more.

12 And I think this concern and worry and
13 whatnot will continue. I think it's just going to
14 remain a reality for pregnancy registries. So I
15 think in advising companies on setting them up, it
16 will be important to emphasize the need for making
17 sure you know the status of a woman's pregnancy at
18 the time she enrolls as well as meaningful
19 discussion of this issue of trying to get her to
20 give written release with her signature on it.

21 And our suspicion is some of it is women
22 are just worried that somehow the data will be

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

136

1 used against their baby, but I suspect another
2 part of it is, you know, she signed up because she
3 was worried. If you contact her after the baby is
4 born and she sees the baby is fine, that changes
5 her motivation.

6 And so one of the issues that we
7 struggle with is trying to get her to sign the
8 forms before the baby is born. And then you've
9 got the clock ticking in terms of how long is that
10 signature valid. So it's a very delicate dance.

11 We started for the last two or three
12 years to encourage the research assistants when
13 they talk to her at enrollment to tell her "We are
14 going to ask you to sign for the release of these
15 materials." And if a woman says at that time, "I
16 really don't want to do that," then we don't
17 enroll her.

18 So we've got a third have said, "Yes,
19 I'll give you permission to do that." And then
20 when the chips are down, they won't do it. So
21 it's a recurring constant, I think.

22 DR. TASSINARI: I think, Dr. Conlin, you

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

137

1 had a comment?

2 DR. CONLIN: I did. And it might not
3 flow completely well with what is being discussed
4 now. But we have a unique population, I would
5 say, at the military. And with our active vaccine
6 registries, I think over time, we have really seen
7 a change in enrollment.

8 I think when we started with smallpox
9 more than ten years ago, there was a concern about
10 that vaccine. So people were eager to enroll and
11 eager to participate. The preventive medicine
12 side is happy that we decreased the number of
13 women that are inadvertently exposed. But then
14 that does decrease your potential pool of
15 enrollees to the registry.

16 And then I think more recently now with
17 the advent of Smartphones and less landlines
18 trying to contact women, it is very easy for them,
19 as someone just mentioned, to enroll because they
20 are worried. But then when you try to follow up
21 with them, they know your number. They're busy.
22 They're not as concerned anymore. And it's

1 increasingly easy for them to ignore your calls.

2 And, for whatever reason, they don't
3 want to unenroll or say, "Please don't contact me
4 again," but a lot of time and resources are spent
5 trying to contact women that are no longer
6 motivated to participate.

7 DR. TASSINARI: Thank you. I would
8 actually like to swing back to the question that
9 started us off here with Tina because if, in fact,
10 the definition of the term "prospective" is a
11 moving target and we're using that definition as a
12 central piece of how we define a pregnancy
13 exposure registry, what is that doing for our
14 registries? And is this something that we need to
15 more precisely define, define differently? How
16 could we, you know, move forward if this is the
17 case? Where is the line?

18 DR. DANA: This is Adrian Dana. I think
19 there is one place where we should perhaps make a
20 distinction. And that is between drugs that are
21 specifically indicated for use in pregnancy, like
22 influenza vaccine and other drugs that either just

1 because the mother has a condition that needs to
2 be treated or there's just a complete inadvertent
3 exposure, you know, they didn't know they were
4 pregnant and they got exposed.

5 So I think that we have an opportunity
6 for drugs that are actually indicated in pregnancy
7 to truly enroll these women before they are on the
8 drug or before they are exposed. So I do think
9 that distinction is important because, although we
10 may not have maximized that opportunity, we do
11 have an opportunity for a true prospective
12 enrollment in those particular cases where we can
13 enroll before exposure at least. Otherwise, it is
14 sort of a slippery slope. And we currently are
15 just saying, "Well, before we know, you know, that
16 a prospectively enrolled patient is one who is
17 enrolled before we know the outcome."

18 DR. GREENE: Mike Greene. As a
19 practicing obstetrician, there are real issues
20 with prospective enrollment for medications that
21 you are supposed to be using during pregnancy.

22 The immediate question that comes up in

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

140

1 the patient's mind is "What do you mean you need
2 to find out whether this stuff is safe? I thought
3 you said you were giving it to me because it is
4 good for me and it is going to protect me from"
5 you name it: influenza, pertussis, my baby from
6 pertussis. So there is a mixed message there. And
7 we have to be very careful how that is perceived
8 by our patients.

9 DR. TASSINARI: Yes, Tina?

10 DR. CHAMBERS: Tina Chambers, changing
11 topics, but I agree with that totally. That's a
12 big communication issue of how you get that across
13 to the patient that it's for the greater good. A
14 question about challenge in design of pregnancy
15 registries is how to know what is an appropriate
16 sample size. So Mike brought up the issue
17 previously of, you know, maybe the success of a
18 pregnancy registry for a high-risk drug is that
19 you don't enroll anybody.

20 But the thing that we struggle with in
21 our work is trying to be clairvoyant about what
22 the number of exposed pregnancies is going to be.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

141

1 And I think that is a challenge and maybe
2 something that could be addressed in terms of
3 identifying better ways of kind of monitoring the
4 landscape for the number of exposed pregnancies
5 that are taking place to determine if a pregnancy
6 registry is meeting the mark or not meeting the
7 mark and if the sample size that is developed for
8 a pregnancy registry is realistic.

9 COL COSTER: Trinka Coster here. Yes. I
10 think that the kind of work that we do and I know
11 that the VA does and the sentinel folks have done
12 I think could probably assist with the registries
13 in knowing what the exposure, whether it's
14 accidental or intentional, is of a pregnant female
15 to a particular drug, especially if it's a new
16 signal put out or a new alert by FDA put out, you
17 can then have a nice marker of data saying what
18 was the exposure rate before the FDA alert went
19 out and what is the exposure rate after the FDA
20 alert out, just on drug utilization, to kind of
21 know if you're doing a good job or not.

22 And then also what Dr. Greene had

1 mentioned is, you know, did we register everybody
2 that we could. I think, again, you can look at
3 the exposure of your pregnant females in large
4 databases and just ask, you know, are we seeing
5 what we would expect, you know, one percent
6 exposure rate and are we really seeing that and
7 that would translate to no. Then we wouldn't
8 expect anybody to register based on prior studies
9 that, you know, you wouldn't find that.

10 So I think there's a use for still
11 having the registries be the gold standard. You
12 know, is this a problem due to this drug but using
13 the observational and large databases to kind of
14 assist with what is the exposure out there as well
15 as even messy, unvalidated outcomes, maybe
16 perhaps, to give a ballpark figure of should I
17 publish this or should I not and what are you
18 seeing in your observational databases?

19 DR. GREENE: Mike Greene. I'll refer to
20 one of Allen Mitchell's publications since he
21 isn't speaking up. Where he showed very nicely
22 that when you asked women about medication

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

143

1 exposures, you get an increasing response rate the
2 more specific you get about what medication you're
3 talking about. So if you ask women, you know,
4 "Did you take any medications during pregnancy?"
5 you get a certain response. Then you say, "Did
6 you take anything for colds? Did you take
7 anything for your fever? Did you take anything
8 for headache?"

9 You get more response. "Oh, yeah. I
10 took" so and so.

11 And then when you get very specific,
12 "Did you take any aspirin? Did you take any
13 Tylenol? Did you take multiple vitamins?"

14 Then "Oh, yeah. I took that stuff, but
15 I didn't think of that." So that speaks to how do
16 you know what to expect because there is not a
17 uniform way of collecting the information.

18 And one other point that I'll make is
19 that I increasingly see a lot of women who are
20 taking medications that aren't in the formulary.
21 Okay? And I don't have a clue what's in those
22 things. And they have names that are very warm

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

144

1 and fuzzy, but the content is very fuzzy.

2 DR. MITCHELL: It's Allen Mitchell. He
3 provoked me. Yes. I just want to reinforce
4 Michael's point -- you know, excuse my voice --
5 that when we talk about medications, whether we're
6 talking about an exposure of interest or a
7 potential confounder or risk modifier, we really
8 need to know information about the full complement
9 of exposures, which includes OTCs, herbals,
10 supplements. And God knows what's in those. We
11 also need to know about periconceptual folate. I
12 mean, if we are looking at birth defects, it is
13 hard to imagine a study that doesn't have
14 information on periconceptual folate,
15 particularly where you have upper SES women
16 preferentially enrolling where the rates of
17 exposure may be higher, because that clearly is a
18 risk modifier, if not a confounder.

19 So, you know, I think how you asked the
20 question is certainly an issue. I think just
21 while I'm thinking about it, in terms of the size
22 of a registry, there are the issues that Tina and

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

145

1 others have raised about trying to predict what is
2 a useful size, but I also think that it's
3 unrealistic to imagine that one could have a
4 registry in sufficient time to be useful, I mean,
5 less than 30 years, where you would have enough
6 exposures to be able to identify risks and safety
7 for very rare defects. And, in fact, I would
8 argue that for very rare defects, there may be no
9 studies that can provide usable information.

10 The flip side of that is for very rare
11 defects, the public health implications are
12 minimal. We worry about defects that occur in 1
13 in 1,000 women. If the risk of a defect that
14 normally occurs in 1 in 10,000 is tripled, we are
15 still talking about 3 per 10,000. It is certainly
16 devastating for the affected patient, but in terms
17 of a public health issue and a regulatory issue,
18 it seems to me that it has less importance.

19 So I think that as we think about
20 pregnancy registry, -- and I'll talk to this point
21 tomorrow -- the most useful aspect is for
22 reassuring that we're not dealing with a

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

146

1 Thalidomide or an Accutane. And then the size
2 issues become problematic given costs and time as
3 we try to hone down on more specific malformations
4 and particularly rarer malformations.

5 DR. YAO: I would like to ask the panel
6 off of what Dr. Mitchell has just said your
7 thoughts, your opinions about, okay, so we're not
8 going to be able to do something for 30 years. And
9 we're not going to pick up necessarily the ultra
10 rare. So what can we do? How can we modify the
11 current state to maybe decrease the time, maybe
12 decrease the patients?

13 I think that Dr. Holmes' presentation is
14 very compelling regarding the use of a concurrent
15 control group. I think that if we're talking
16 about the efficacy side, we ask for control
17 studies to try and cut down on the number of
18 patients that you need to establish efficacy. Can
19 we do that in a way on the safety side post-
20 marketing that would help us decrease the time or
21 number of patients overall to assess a signal? So
22 I would like to hear the panelists' comments about

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

147

1 that.

2 DR. HOLMES: Let me give you my
3 comments. It's Lewis Holmes from the North
4 American AED Pregnancy Registry.

5 When you are beginning your pregnancy
6 registry, your challenge is effective marketing.
7 And the cost of marketing varies quite a bit
8 depending on how aggressive you are. And that was
9 one of our real dilemmas. We were fortunate in
10 that in our surveys in Boston, we knew that about
11 1 in every 250 women at delivery was taking one of
12 these drugs. So it's a relatively common
13 exposure.

14 But, even so, mailing lists of the
15 Society for Maternal/Fetal Medicine is an expense.
16 Sending a letter, instead, to all the members of
17 ACOG is a huge expense; same for the neurology
18 groups, the epileptologists versus all
19 neurologists; sending advertisements to primary
20 care physicians, who prescribe Topiramate for
21 migraine, not for epilepsy. I mean, you just face
22 endless theoretical possibilities at how to reach

1 people.

2 And there's a huge delay before you
3 begin to get enrollment. And you don't really
4 know why anything has worked. Ultimately, it
5 became apparent that there is a group of people
6 that we call cheerleaders, who are the folks who
7 are really aware of the registry and really
8 actively encourage their patients to sign up. And,
9 obviously, you would have loved to have found the
10 cheerleaders in the beginning. And you could send
11 all of your mailings to those people and not the
12 thousands of folks who are going to throw it away.

13 So if you're trying to make a registry
14 more efficient and get answers sooner, it's the
15 front ending, more money for marketing to me would
16 be -- if I had to do it all over again, I would
17 want to have more money so we could really start
18 spreading the word faster, beginning the process,
19 ultimately finding those people who are helpful.
20 And that would be my advice to anybody. Don't do
21 it on the shoestring because the chances are it
22 will drag out and wear out everybody's patience

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

149

1 and tolerance and never get anywhere.

2 DR. TASSINARI: It sounds like we may
3 need to phase out the word "passive" in our
4 description of what these programs are designed to
5 do because I think, as you say, it really all
6 depends on how well you get off to a start.

7 Tina?

8 DR. CHAMBERS: Adding to what Lew said
9 in responding to your question, I think that it
10 depends on the drug and the disease, too, and how
11 commonly it is going to be used. So maybe the
12 realistic, you know, perspective on a drug that is
13 going to take 30 years to accumulate enough
14 exposures to say something is to set the goals of
15 the registry to something that you can do in an
16 interim or more reasonable period of time.

17 And I think it is important not to lose
18 sight of the fact that pregnancy registries aren't
19 just about major birth defects. They're about
20 looking at a spectrum of outcomes that we know
21 that known human teratogens are typically
22 associated with. And I think that is one of the

1 great advantages of pregnancy registries, giving
2 an early sort of snapshot view of is there an
3 increased risk for reduced birth weight, is there
4 an increased risk to the extent that you can look
5 at it, spontaneous abortion or preterm delivery?
6 And if you are looking at that broader range of
7 outcomes, it becomes increasingly important to be
8 able to have an internal comparison group.

9 DR. HERNANDEZ-DIAZ: I think that's a
10 good point. I'm so far being realistic with the
11 goal. So if because of the use you can only
12 possibly enroll 50 women, then that's what you can
13 do. And then the question is, what would be the
14 goals of that registry and how to report with a
15 confidence around what we can report. But
16 following up on your question about controls, such
17 as wanting to add to the internal non-exposed
18 control group that in the disease-based registry
19 or multi-drug registries for similar indications,
20 one of their advantages, I think, is that they
21 allow us to assess comparative safety, comparative
22 effectiveness. That is such a hot topic. So they

1 will allow us to compare drugs with the same or
2 similar indication. And I think that has the
3 advantage of having the internal control group
4 with the same methodology, same diagnosis of the
5 outcomes, but, you know, that's another thing.

6 There are two more advantages to them,
7 that, first, you have women with the same
8 indication so that they will have a more similar
9 background of certain outcomes to the confounding
10 because of indication will be lower. And also
11 they may respond to the clinically relevant
12 questions of which medication to use to treat
13 these specific women when we are dealing with
14 diseases that treatment is necessary for pregnant
15 women. So when possible, I understand it is not
16 possible for all registries, but having these
17 multi-drug registries I think add these additional
18 advantages.

19 And I know that they are logistically
20 complicated for the reasons mentioned. But I
21 think that could be another thing to consider for
22 controls.

1

2 DR. BERLINER: I just wanted to comment
3 on some of the things that I heard that seemed a
4 little contradictory. So one thing I heard is
5 that women are enrolling in these registries
6 because they're worried, which sounds like they're
7 misunderstanding that the registry will help them
8 personally versus contribute to knowledge and then
9 the other issue of that people are -- you know,
10 that maybe physicians don't even want to mention
11 the registry because it will make the patients
12 worry.

13 And so I sort of wonder what the best
14 practices are, you know, and having gone through
15 pregnancy myself, you know, what the best
16 practices are where you have a conversation with
17 your doctor at the time that you are thinking of
18 getting pregnant or you find out you are getting
19 pregnant, you are pregnant, about whatever your
20 medical conditions are and what is known about the
21 risks and benefits of continuing your medication,
22 what the alternatives are, what the potential

1 risks to the fetus are. And I think that
2 conversation has to happen in every single case.
3 And so part of that discussion could be or should
4 be what is unknown about the risks and then if
5 there is a registry inviting the person to
6 participate, not because it will help them but
7 because it will help other people.

8 And, you know, I know from other
9 registries I worked on on, really, widely varying
10 topics that, really, people are -- you know, that
11 they are altruistic and that they do want to
12 participate in that if they really understand. And
13 so I am just wondering about other people's
14 thoughts on that.

15 DR. GREENE: Mike Greene. Some of this
16 is anticipating a little bit of what I am going to
17 address this afternoon in my talk, including a
18 recommendation for a way of possibly improving
19 registration of exposures in registries, but one
20 method that I would like to mention that Allen did
21 very successfully with the Accutane registry was
22 to say to women who were receiving prescriptions

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

154

1 for Accutane, you know, you're not supposed to get
2 pregnant when you're taking this stuff, but with
3 the prescription, it says, but, you know, if you
4 accidentally do, please call 1-(800). And how did
5 you do that, Allen?

6 DR. MITCHELL: Well, actually it wasn't
7 quite that.

8 DR. GREENE: Okay.

9 DR. MITCHELL: Now you are prompting me
10 to have to recall something. So we're in problem
11 state.

12 What we did was we came up with I think
13 what was the first direct-to-consumer
14 solicitation, where included in the Accutane
15 package was an enrollment form. And the idea was
16 for women to enroll in advance of potential
17 pregnancy. Ideally, they would, you know, enroll.
18 And we made it look as much like a toaster rebate
19 coupon as we could, consistent with IRB and other
20 regulations. And we paid them \$10 for the effort.
21 And the idea was to encourage them to enroll and
22 then be followed. And we randomized them to

1 different follow-ups. And then we were able to
2 identify those who became pregnant. So we had
3 them in the system.

4 I'm not sure that's applicable to a
5 pregnancy registry. I hadn't thought of it in
6 that context. I mean, the idea of enrolling all
7 women who are potentially at risk for pregnancy
8 seems overwhelming for a pregnancy registry and
9 then, you know, thinking, well, if they are
10 exposed to a given drug, that might work for a
11 universal registry. If there were one registry
12 into which all women would fall if they were
13 exposed to drugs A through Z, it might work. I'm
14 not sure it would work in the context of
15 recruitment here.

16 DR. CRAGAN: This is Jan Cragan. I
17 wanted to get back to part of the comments on
18 sample size and experience of the North American
19 AED Registry when two or three cases of cleft
20 showed up in the first couple of hundred or so
21 exposures to lamotrigine. There were a lot of
22 discussions. And that was not an easy discussion

1 about, do we release those findings? What do they
2 mean? You know, what is this? And now we have
3 seen the rates go down quite a bit. And there is
4 an I think currently real interest in, oh, well,
5 this registry has produced a lot of information.
6 And now it's getting big enough we can look at
7 these individual defects and we can say more about
8 the risks of these drugs, which is true.

9 But I think I also have reservations
10 about continuing to do that too much because you
11 will see these kinds of spurious things that come
12 up that you don't know quite what they mean. And
13 when that happens, then you are in the position of
14 but we have this information that might indicate
15 it is a risk. We can't just keep that to
16 ourselves. You know, people have a right to know
17 what we know. And this is all we know right now
18 and such.

19 So I think it is important to keep the
20 goals of these registries in mind in the context
21 of -- and I know tomorrow is about alternative
22 approaches and other kinds of data sources. But

1 to keep the role of the registries in the context
2 of what other kinds of studies can be done to
3 better address certain topics and that maybe these
4 are good for generating questions that can be
5 addressed through other means. And that's partly
6 GlaxoSmithKline had a registry solely for
7 lamotrigine. And when it closed, part of the
8 reasoning was that there are other methods and
9 other data collections out there that can look at
10 this better than the registry can at the moment.
11 So I think that is an important thing to keep in
12 mind when looking at what is the goal of our
13 registry and how large does it need to get.

14 DR. TASSINARI: I'd like to get back to
15 that just for a minute, but, Dr. Honein, you had a
16 comment?

17 DR. HONEIN: This is Peggy Honein. And
18 I just wanted to bring up the issue of adverse
19 outcomes for a pregnancy registry and the
20 importance of having it where possible. I think
21 there is a real challenge with the registries only
22 capturing adverse outcomes on the date of birth

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

158

1 and really missing many of the birth outcomes and
2 essentially all of the development. And I just
3 would like to be a part of that conversation about
4 how we have --

5 DR. TASSINARI: Peggy, you were breaking
6 up just a little bit at the end. What was that
7 last piece?

8 DR. HONEIN: Sorry. The connection.
9 Okay. I'm just wanting to think about how
10 pregnancy registries can get all adverse pregnancy
11 outcomes, which is certainly what the moms want to
12 know, just for the --

13 DR. HOLMES: Peggy, this is Lewis Holmes
14 from the North American AED Pregnancy Registry. We
15 have done studies on cognitive development in
16 children exposed to anticonvulsant drugs. And
17 that is a real challenge. My colleagues in
18 developmental psychology recommended that the
19 children be at least six and a half years old at
20 the time they are evaluated. We found that it is
21 a very labor-intensive process. You need to get
22 information on the mothers' and fathers' IQs and

1 the comparison child's parents as well as the
2 child, incredibly expensive.

3 And if you are enrolling women during
4 pregnancy for a pregnancy registry, you do have at
5 the end, at that postpartum interview. You've got
6 theoretically a sample size that could be
7 recruited six years later. So in that sense, it's
8 a valuable potential resource. But it is an issue
9 of pick the things, the questions that ought to be
10 asked. For example, in anticonvulsants, we would
11 say pick the drug that is associated with a higher
12 rate of malformations because that is the one that
13 is probably going to have a higher rate of being
14 associated with developmental issues. Find a
15 bucket of money somewhere. Wait six years. And
16 do it.

17 And that is not a model that is easy to
18 move and to have in one office. You would almost
19 want to have collaborations between us and, say,
20 developmental psychology groups that are better
21 set up to do the post six and a half-year-old
22 follow-up.

1 Our system is very dependent on funding
2 that is just very fragile. And it's hard to
3 imagine how we could be fortunate enough to have
4 resources that are ready to go as soon as these
5 children get to six and a half. So I think it's a
6 wonderful goal to take the additional perspective
7 of how many of these children have problems in
8 learning, but I'm just not sure how realistic it
9 is given that everybody is worried about just
10 being able to pay their rent.

11 DR. IYASU: So since we're talking about
12 challenges, I wanted to go back to the issue of
13 sample size. You know, sample size, I guess
14 several people have pointed out that, you know,
15 it's determined or it's based on what the question
16 is that you're asking. And so we get protocols or
17 proposals that would assume that sample size based
18 on sort of detection of a twofold increase in
19 measurement information that may be spanning
20 multiple organ systems. And that, you know,
21 sometimes is very difficult to interpret because
22 thinking about how teratogens would work, you

1 know, you don't think of them as causing multiple
2 issues with multiple sort of organ systems. So
3 sort of what is the trade-off in terms of powering
4 to measure malformations as a group versus
5 specific, you know, defects or organ systems
6 because that is a challenge that we have in terms
7 of not only pregnancy registries but also in the
8 interpretation of the data that you may get out of
9 these registries. So what does it mean if it's,
10 you know, 20 percent increase or 30 percent
11 increase over background or whatever reference
12 group you are looking at?

13 DR. CHAMBERS: So I think that's a
14 really great point. And it's even further
15 complicated by the common situation where the
16 pregnancy registry is focused on a drug or a
17 vaccine that isn't used continuously throughout
18 the first trimester so you're not just talking
19 about sample size of exposure in the first
20 trimester. You're talking about sample size of
21 exposure at a critical window for embryonic
22 development, for an outcome that you're interested

1 in looking at. And I think it comes back in
2 pregnancy registries where the sample size that is
3 feasible or obtainable is smaller, that in terms
4 of major malformations, they function as signal
5 detection mechanisms and, as Jan says, they
6 generate hypotheses that can be tested using other
7 methods that really are better powered to look at
8 specific birth defects.

9 DR. MITCHELL: Yes, two things. To go
10 back, Solomon, if I can, to the previous
11 discussion, -- and I'll return the favor of
12 quoting Michael -- when we talk about what is a
13 reasonable goal for a pregnancy registry, Michael
14 uses the term "the long shadow of DES." And, to
15 quote a previous government official, there are
16 the known knowns and the unknown unknowns.

17 And I think that those of us who have
18 been involved in this area for some years
19 recognize that something like DES is not going to
20 be identified in any in any reasonable system or
21 any reasonable time. I mean, if it takes 18
22 years, at a minimum, to manifest the problem, by

1 definition, you are going to have wait 18 years
2 from exposure.

3 So I think, you know, on the qualitative
4 side of what you can identify, that's the extreme.
5 I think the issues of development, I would echo
6 what Lew said, but I would add more to it. And
7 that is I don't think it can be solved just with a
8 bucket of money because if you are going to follow
9 up kids to age six and a half, you have to be very
10 aware of intercurrent exposures, which can affect
11 development. So it's not simply a matter of going
12 back to those kids. You have to stay in touch
13 with them and repeatedly interview the parents and
14 so forth.

15 And so I think we have to be careful
16 about what we define as reasonable goals. And I
17 would argue that that ought to be driven as much
18 as possible by public health concerns. So the
19 more common outcomes, the more common disabilities
20 are of most concern.

21 And then we have to look at what is
22 feasible. I mean, are we going to be trying to

1 identify risks of autism for every drug that is
2 being marketed. That is a real tough challenge.
3 And I think we need to be able to accept the fact
4 that there are certain things we may not be able
5 to know or we may know them so much later than we
6 would like.

7 And, just as a final point, in terms of
8 the size of the registry, I'll echo what other
9 people have said. And I don't think it ought to
10 be understated. And I'll mention it again
11 tomorrow. The value of a pregnancy registry apart
12 from the other pregnancy outcomes that -- we're
13 focusing on birth defects, but, as Tina points
14 out, there are a lot of other pregnancy outcomes,
15 adverse outcomes, of concern that a pregnancy
16 registry can very effectively identify, I would
17 argue.

18 In terms of birth defects, we really
19 need a sort of frontline system to assure that we
20 don't have Accutanes and Thalidomides out there.
21 When a drug is brought to market, we really don't
22 know in the human condition whether that drug may

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

165

1 be an Accutane; a Thalidomide; or even a valproic
2 acid, which is sort of intermediate. So I don't
3 think that we ought to dismiss their value, but I
4 think we ought to be very careful about
5 identifying what it is we think they can produce.

6 DR. TASSINARI: Well, in the course of
7 your conversation, some of you may have noticed we
8 switched to question 2, which asks, based on some
9 of the challenges and advantages that we do know
10 about registries, what are your recommendations
11 for overcoming some of these challenges that we
12 have been talking about in the last few minutes?
13 So, Allen, I don't know, you know, based on those
14 comments whether you have some thoughts about the
15 kinds of things we should be thinking about to
16 make sure that the pregnancy registry still is an
17 effective or a most effective tool that we have to
18 choose from when we are trying to get some of this
19 data.

20 DR. MITCHELL: Yes. As anyone who knows
21 me knows, I am never shy about answering a
22 question, but on this one, I think I would defer

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

166

1 to many more experts in the room who have, really,
2 hands-on experience with the registries, because I
3 think you're now dealing with sort of the
4 qualitative aspects of operating a registry. And
5 that's something with which I am not as familiar
6 as others.

7 DR. HOLMES: This is Lewis Holmes again
8 from the North American AED Pregnancy Registry. I
9 didn't say in my presentation, but I would predict
10 for the FDA and others that if there's not
11 sufficient attention paid in pregnancy registry
12 design to inclusion and exclusion criteria, you
13 are going to be presented with epidemics of
14 muscular VSDs, epidemics of hydronephrosis
15 detected during pregnancy by ultrasound because
16 those designing the study didn't really go through
17 the process of either agreeing what is a
18 malformation and what is not. And they don't have
19 an internal comparison group. And you're going to
20 have that happen. And then you're going to be
21 left with, what do we do with this now? You're
22 basically saying you've got to start all over

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

167

1 again and do it right.

2 So my suggestion is that you guys need
3 to put more teeth into the recommendations in
4 terms of saying you've got to do this, you've got
5 to do this, so that you have something well-
6 designed or it doesn't get blessed by the FDA.

7 DR. CRAGAN: This is Jan Cragan. So
8 along that line because I have had a similar
9 feeling for a long time that, you know, there has
10 been guidance put out, we know what the
11 methodological issues are, there are some
12 registries that are dealing with many of those
13 that have comparison groups and such, and that
14 it's sort of time to up the bar a little bit and
15 that FDA should be able to say, rather than just
16 "You need to do some post-marketing monitoring of
17 pregnancies in order to market this drug, to be
18 able to say, "And you need to do it of this
19 quality" or "in this way" or whatever.

20 And I'll just share this. It has some
21 parallels, but it's not entirely. But one of the
22 things that has happened in the birth defects

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

168

1 world is the state birth defects programs -- and
2 CDC funds some of those but not all by a long
3 shot, and they have gotten together and, you know,
4 many years ago wrote a guidance, guidelines for
5 conducting birth defect surveillance that has been
6 very helpful to new programs coming along and
7 such. And we have, you know, some programs that
8 are just getting started, some that have been
9 there for a while, some that do a great job.

10 But what they have done over the last
11 two or three years is to get together and try to
12 move from guidelines to standards. And so the
13 programs themselves, it has been with our help,
14 our expertise. We have helped with coordination
15 and stuff, -- but it's the programs themselves
16 putting this together -- have started to come up
17 with standards for the quality of the data they
18 collect. And now they are working on the utility
19 of the data they collect and meant as a self-
20 assessment for the programs. It's not a grading
21 that gets published and such but as a self-
22 assessment to see where they are.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

169

1 And so, you know, they have some
2 standards for -- you know, if you are going to do
3 birth defect surveillance, you at least have to do
4 this much. And then they have standards that --
5 well, most of our programs probably fall within
6 this range. And that is kind of where everybody
7 is. And then they have sort of the gold standard
8 of, you know, this is what everybody should be
9 striving for.

10 And, as I said, they've come up with
11 that for themselves. And I don't know if that is
12 even possible in this range, but if there were
13 some similar sort of set of standards about post-
14 marketing surveillance for medications in
15 pregnancy that FDA could refer to and say, "You
16 need to conduct surveillance to market this drug.
17 You need to do it at least a certain standard. And
18 here are some programs already out there doing
19 it," something like that might be helpful. I
20 don't know.

21 DR. HERNANDEZ-DIAZ: Did you ask would
22 we think about where measures can be best? I

1 think we would all agree that they are poorly best
2 as the first line of defense against Thalidomides.
3 So that we don't have another Thalidomide program.
4 So with some 100 women enrolled, you can rule out
5 huge increases of major malformations, although I
6 think that because they can enroll specifically
7 exposures to medications that may be, at least at
8 the beginning, rare. They can enroll them even
9 before large databases that need some years to
10 have women enrolled in them, have the pregnancies,
11 and clean the data. So I think there they can
12 clearly be the best.

13 And I think, as you step away from that,
14 that door is specifically fixed or even
15 development problems, you not only need a larger
16 sample size. But then the validity of every step
17 that we discuss from perspective, personal
18 perspective, to evaluation of the outcomes, et
19 cetera, then you need to have better and better
20 methods. So it gets more complicated if you try
21 to get to more rare events or long-term events.
22 And then you move away from the idea.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

171

1 Now, where to put the line, I think it's
2 up to discussing, but I think we all agree where
3 the extremes are.

4 DR. TASSINARI: And it's the middle
5 where we usually play.

6 DR. SAHIN: I have a question for Jan
7 Cragan. The Metropolitan Atlanta Congenital Birth
8 Defects Program is one of the most commonly used
9 comparison groups. Could you comment? Please
10 give us your thoughts on the appropriateness of
11 using this as a comparator group. Thank you.

12 DR. CRAGAN: Sure. So I work in the
13 Birth Defects Branch at CDC, and I am currently
14 Medical Director of the Metropolitan Atlanta
15 Congenital Defects Program. And that's a
16 convenient, commonly used reference for how
17 frequently birth defects occur generally, not just
18 by pregnancy registries but by lots of activities,
19 mostly because MACDP collects data on all
20 malformations, genetic conditions, chromosomal
21 anomalies. So it's a very broad ascertainment.
22 And it's been in existence since the late 1960s.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

172

1 So it's very longstanding with very stable
2 prevalences, et cetera. But I have some real
3 issues with it being used as a direct comparator
4 for pregnancy registries.

5 The methods are very different. MACDP
6 is a retrospective ascertainment. We identify
7 children and pregnancies with birth defects by
8 reviewing medical records at local pediatric and
9 birth hospitals, prenatal care sites,
10 maternal/fetal medicine departments, and such. We
11 go to a few pediatric specialty clinics but not
12 all of them. And it is mostly a hospital-based
13 system. So for a child to be recognized, they
14 have to have either had surgery or required
15 hospital care for their condition.

16 It's also purely a truly population-
17 based ascertainment. So mother has to be a
18 resident of the central counties of Atlanta at the
19 time of delivery to get included. And we know
20 that the population of Atlanta is not
21 representative of the population of the general
22 U.S. of all pregnant women or certainly not of all

1 women who have a certain condition or who may take
2 a certain drug. So I think the population
3 characteristics may differ.

4 MACDP ascertains defects up to six years
5 of age. And so, as Lew was pointing out, the
6 prevalence can be very different depending on the
7 timeframe. And most of the registries that I know
8 of either collect information on the newborn or
9 within the first year of life.

10 And so I think, for all of those
11 reasons, you wouldn't expect the prevalences seen
12 by MACDP to be similar or to be exactly the same
13 as what is ascertained by a registry. What I have
14 tried to tell registries is that they shouldn't
15 make direct comparisons, saying, you know, "Is our
16 prevalence the same as MACDP's?" If they don't
17 have an internal comparator, then they can review
18 the literature and look at prevalence estimates
19 that have been published. And MACDP is one of
20 them, but it is not the only one out there.

21 What I do think MACDP is helpful for is
22 this kind of idea of applying a straight case

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

174

1 definition to what is a birth defect and what are
2 the inclusion and the exclusion criteria. And
3 there are registries that use our criteria because
4 they're well-documented and they can call us and
5 ask if they have questions about particular
6 defects. And I think that application of a
7 specific case definition is very helpful. And
8 it's fine to use MACDP's case definition, but I
9 don't think you would expect the prevalence seen
10 in MACDP necessarily to be the same as what is
11 seen in a registry.

12 COL COSTER: Trinka Coster here. One
13 comment on how to maybe get more people aware of
14 the benefit of registries is do some of the
15 marketing that we have done with meaningful use,
16 at least in CMS, for following metrics. We have
17 also done it with partnership with patients. So,
18 for example, you know, opioids. You know,
19 everybody is talking about opioids, opioids. How
20 many people are on it? How many people are on
21 this dose? And essentially everybody is
22 developing metrics for that.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

175

1 I could imagine if you decided on a drug
2 class that you were considering as concerning and
3 you pushed that up to get a meaningful use or
4 partnership with patients advertisement that
5 everybody develops a metric for did you have the
6 females, yes or no told about the registry. And
7 at least you're getting then a metric on how many,
8 you know, people complied with, you know, the
9 family physicians, you know, everybody else on
10 talking about this. And it could be a safe drug
11 just to get females used to the fact that we have
12 registries, we monitor this stuff, and then you
13 kind of get a herd effect of that kind of passing
14 over to other registries that you have.

15 But I know that we are all inundated at
16 the health care places with these kinds of
17 initiatives. But once -- I mean, they really do
18 take hold. And it really kind of does get
19 everybody stepping in line with doing something
20 like that.

21 DR. ALBANO: This is Jessica Albano. I
22 think one thing that would be helpful is to have

1 some input for industry, particularly, about what
2 is considered appropriate versus potentially
3 promotional in regards to awareness activities. I
4 think that can sometimes be a big stumbling block,
5 not doing enough or really much of anything as far
6 as awareness to increase enrollments in a registry
7 for fear of promoting use in pregnancy when it's
8 not indicated for that.

9 DR. CHAMBERS: This is Tina Chambers.
10 And, to follow on Jessica's comment, I think that
11 really is important, not only understanding what
12 you can do, but, going back to Mike's comment
13 earlier, maybe some guidance for industry,
14 especially for industry-based registries, about
15 how to communicate the existence of a pregnancy
16 registry in such a way that it isn't perceived as
17 negative for the drug.

18 DR. TASSINARI: So I think we've heard
19 several times about recruitment efforts, awareness
20 efforts. I think that is a great term. Are there
21 any other means to address this, what appears to
22 be a constant issue of struggle to enroll in a

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

177

1 registry? I'm also struck, too, by the fact that
2 very often we see pregnancy exposures reported in
3 other systems when we know that there is a
4 registry available. So it continues to raise this
5 question. Is it just awareness or is there
6 something else happening here that we should look
7 at and address?

8 DR. MITCHELL: It's Allen Mitchell. I
9 don't know the answer to it. I do know
10 historically practitioners have been very wary of
11 getting anywhere near the notion of anything I
12 prescribe might do your baby harm. I think part
13 of that is the litigious nature of our legal
14 system. And, you know, part of it is I think from
15 just a clinical standpoint, as Michael said, the
16 clinicians' reluctance to suggest that there is a
17 problem when there isn't. And how you overcome
18 that is tricky.

19 But I do think that educating
20 practitioners about the need to collect data not
21 being a sign of danger, not being a sign of
22 imminent harm, it's not an easy message to

1 communicate. And there are others who are much
2 more expert at it.

3 But I think that so many practitioners
4 when you talk to them about -- even today, I think
5 it's less a problem, but it's still a problem.
6 When you talk to them about drug use in pregnancy,
7 they really don't want to raise that subject of
8 any kind of potential risk.

9 And, you know, a classic example is the
10 SSRIs, where you've got a woman in front of you
11 who is incredibly anxious and depressed and now
12 you're going to raise the risk in her mind about
13 the drug you're taking for your anxiety. So, I
14 mean, that's sort of the arc typical worry, but I
15 think it's a major task.

16 DR. GREENE: Mike Greene. Melissa, your
17 question is very pertinent. About a year or two
18 ago, the National Toxicology Program endeavored
19 upon a review of the potential pregnancy effects
20 of all chemotherapeutic agents that are used for
21 cancer treatment. And one of the biggest problems
22 that they encountered was scrounging together all

1 of the case reports. And in that situation,
2 although the medications are likely to be
3 teratogenic, many of them, there's no central
4 repository for information about them.
5 Fortunately, cancer during pregnancy is relatively
6 uncommon. So there aren't a huge number of
7 exposures. But there is no central place to find
8 information about the consequences of those
9 exposures.

10 All of the reports in the literature are
11 either single case reports or very brief case
12 series. The quality of the reporting was very
13 variable, at best. In many cases, we couldn't
14 figure out what the gestational ages at exposure
15 were, what the cumulative doses were, what
16 concomitant medications may have been given. So
17 these are problems that are very germane, even
18 when you're giving out medications that you know
19 are likely to be teratogenic, but you don't have a
20 heck of a big choice because the patient is very
21 sick.

22 DR. TASSINARI: Any thoughts on how to

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

180

1 address our issues of loss to follow-up or absence
2 of data?

3 DR. MITCHELL: I don't see Tina or Diane
4 saying anything, but I think one of the approaches
5 I know OTIS uses is basically establishing a
6 relationship with the consumer, with the patient.
7 I think if you are working through the physician
8 as an intermediary, you are dealing with an
9 incredibly difficult challenge. And it gets worse
10 as time goes on because physicians have a lot of
11 other things on their plates to worry about than
12 chasing down the outcome of patients. But when
13 you have patients who are enrolled in the registry
14 directly by the registry and they have what they
15 perceive to be a relationship with the registry, a
16 personal relationship, I think you can get loss to
17 follow-up rates of, what, less than five percent.
18 So it can be done.

19 DR. TASSINARI: What is a reasonable
20 loss to follow-up rate in a typical registry? Is
21 it in the 25 percent range? Should we expect, you
22 know, 50 percent? What could it or should it be?

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

181

1 DR. HERNANDEZ-DIAZ: Yes. That is a
2 good question. I think probably OTIS has the
3 record of the lowest because women are calling.
4 Right? So the women who are enrolled have shown
5 an interest already.

6 In the North American Anti-Epileptic
7 Pregnancy Registry, it's more about 15 percent but
8 the same thing. Women call to enroll. And even
9 when prescribers sometimes recommend them to
10 enroll, they are the ones who call.

11 And also perhaps it also helps to have
12 this several calls during pregnancy, say, at seven
13 months and then postpartum so that they keep in
14 contact.

15 And another thing that may help is if
16 you wait until delivery to ask mom to complete
17 forms and send you the forms, it may not be the
18 best timing right after birth. So if you can get
19 that done a little bit before, at the same time
20 allowing enough time for you to have the records,
21 maybe after two or more months later, that might
22 help, too.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

182

1 DR. DANA: This is Adrian Dana. I will
2 say that, you know, I think there is a big
3 difference between a manufacturer-run registry,
4 where there is a manufacturer contacting a
5 patient, and a registry where there is a health
6 care provider that may, in fact, be their health
7 care provider following up.

8 I will say that we have had a little bit
9 better record and that our loss to follow-up, even
10 from a manufacturer's perspective, is only about
11 30 percent. And I am not sure what the difference
12 is, but we do require that there is a health care
13 provider for enrollment so that we can both
14 contact the provider and the patient, you know, if
15 needed, to try to get that follow-up information.

16 So, you know, obviously what you are
17 striving for is 100 percent, but I don't think
18 that is realistic. And I think that the character
19 of the registry, you know, you will get different
20 rates of loss to follow-up. And depending upon
21 who is running that registry, different rates of
22 loss to follow-up are just going to be the case.

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

183

1 DR. TASSINARI: Well, then, in the
2 closing minutes, I think I would like to move to
3 question 3. And this is really around the topic
4 of looking at the decisions that need to be made
5 when you have a product that would benefit from a
6 registry. And what are the criteria for
7 determining whether we should have a single
8 product or a multi-product or a disease-based
9 registry? And which design is appropriate when?
10 I'm sorry, Michael. Go.

11 DR. GREENE: Mike Greene. So I am on
12 the scientific advisory committee for the
13 ribavirin registry. And we have had to address
14 this recently. For many years, we looked just at
15 ribavirin, but in recent years, there are new
16 protease inhibitors that are increasingly used
17 either with or now instead of ribavirin to treat
18 hepatitis C. And the question now came to our
19 group, you know, should we now start broadening
20 registration, not just for ribavirin exposures but
21 also for protease inhibitors?

22 And it gets very complicated fast

1 because ribavirin is off patent. There are a
2 number of companies that produce it and,
3 therefore, sponsor the registry. Many of the
4 companies now that are producing the protease
5 inhibitors have nothing to do with ribavirin. And
6 they are virtually at this point all still on
7 patent. And it gets very complicated fast as to
8 how do you expand a drug registry just as a
9 practical matter.

10 DR. HOLMES: As I mentioned earlier,
11 Lewis Holmes, the North American AED Pregnancy
12 Registry. Advertising, initial advertising, is a
13 really crucial expense and effort. And the
14 advantage of having multiple products and multiple
15 companies, part of that process is obvious. You
16 know, you have a much better chance to get more
17 support, and you have a much better chance to
18 spread the word more widely because it's not just
19 drug A, drug B, and drug C but, you know, a whole
20 group.

21 We think of anticonvulsants being in the
22 low 30s range, 33, 34. And that's been very

1 helpful.

2 DR. CHAMBERS: So, in my opinion, there
3 are situations like the Anti-Epileptic Drugs and
4 Pregnancy Registry and the antiretrovirals, where
5 it's sort of a slam dunk that a disease-based
6 registry makes a lot of sense. But the scenario
7 that Mike described is probably going to happen
8 more and more often where there is a drug and then
9 there is another one and then there is another one
10 and it happens sequentially. And so, then, how do
11 you go back, then, and revisit the situation of
12 should this be a disease or a cluster of disease-
13 based registries?

14 And maybe the thought there is when you
15 have, you know, a critical mass of several
16 products that are coming to market when the post-
17 marketing commitment or suggestion is made that a
18 pregnancy registry be set up. Should the
19 conversation be suggested, then, to be had with
20 existing pregnancy registries that somehow could
21 be remodeled to address the disease-based
22 approach?

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

186

1 DR. HERNANDEZ-DIAZ: Sonia Hernandez-
2 Diaz. I agree. As I said, I think that there are
3 many advantages from a public health point of view
4 to have multi-drug registries when there is a
5 disease treated with several alternatives. And it
6 improves the validity as well from a math point of
7 view but also logistically when a new drug will
8 come to the market, there will be the network in
9 place to I think -- it will be easier and faster
10 to have information ready for that new medication.

11 Having said that, I understand that
12 logistically that represents making different
13 companies collaborate and then with some of them
14 going generic in a pattern, that may be very
15 complicated. But I think from a purely public
16 health point of view, they generally will make
17 more sense.

18 DR. ALBANO: This is Jessica Albano. One
19 of the other complications is not having a clear
20 understanding from a generics perspective what the
21 obligations are and whether or not they will be
22 required to participate. So certainly for the

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

187

1 brand new products that are already there, but
2 then once they go off patent, you know, is there a
3 clear precedent for how, you know, that
4 therapeutic area moves forward?

5 DR. MITCHELL: Yes. I just want to
6 reinforce what Jessica said and actually extend it
7 a little bit. For a manufacturer whose drug is
8 about to go off patent, that issue becomes very
9 real because the question is, should they be
10 investing in a pregnancy registry when, in
11 fact, the majority of sales, the majority of the
12 market within three or four years is going to be
13 generic.

14 So I would throw at FDA's feet the issue
15 of making generics responsible for their drugs in
16 some way that is equivalent to the sponsor so long
17 as those drugs are being used by pregnant women. I
18 think that's really an issue.

19 DR. CHAMBERS: Just to add to that, I
20 think we're the ones who have the one generic
21 pregnancy registry. At least how it was
22 communicated to us was that they were strongly

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

188

1 recommended that they needed to join the pregnancy
2 registry as a group, which they did.

3 MODERATOR WRAP-UP MORNING SESSION

4 DR. TASSINARI: Well, thank you very
5 much for this morning session. I think it has
6 been very helpful in hearing your experiences and
7 your thoughts, particularly around where we are in
8 this current state. I will ask if there are any
9 final thoughts here in the room. Yes, Mike?

10 DR. GREENE: I would just like to make
11 one other comment, which is that when the basic
12 principles of mammalian teratogenesis were being
13 described in the 1950s and '60s, there was a
14 straightforward correlation in everybody's mind
15 between a drug and a malformation. And if you got
16 a drug that seemed to cause a whole lot of
17 malformations, people sort of dismissed it and
18 said, "Well, you know, maybe that's really
19 confounding by indication, you know. It's the
20 fever that caused all of these different
21 problems."

22 I think that life has become more

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

189

1 complicated as we have learned more about genetics
2 and teratology and we now know more about
3 homeoboxes, genes, and transcription factors that
4 affect the expression of suites of genes that
5 could make it more credible that a variety of
6 congenital malformations could, in fact, result
7 from a single exposure. Life is no longer I think
8 as simple as it was in the 1950s and '60s, when J.
9 G. Wilson was describing the principles of
10 mammalian teratogenesis.

11 DR. TASSINARI: And our colleagues on
12 the phone, any comments?

13 DR. CONLIN: This is Dr. Ava Conlin. No,
14 nothing further for me right now. Thank you.

15 DR. TASSINARI: Okay.

16 MS. MOYER: So we are about to break
17 for lunch. And we will have one-hour lunch break,
18 which is on your own. If you are a panelist and
19 you are participating in the lunch, we have that
20 in a separate area for you. If you didn't
21 participate, you can certainly also use the room.
22 So we will be breaking for one hour. And we will

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

190

1 resume at 1:00 o'clock with the open public
2 comment session. If you have not registered or
3 let us know that you were here and you had
4 previously let us know that you were interested in
5 speaking, please see the registration desk so that
6 you can check in and we're ready for you. Enjoy
7 your lunch.

8 DR. TASSINARI: Thank you very much.

9 (Whereupon, at 12:01 p.m., the
10 public meeting was concluded.)

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Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

191

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Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 1

<p style="text-align: center;">\$</p> <p>\$10 154:20</p> <hr/> <p style="text-align: center;">1</p> <p>1 4:17,19 5:18 16:11 43:12,15 59:3 60:1,19 61:2,16 74:3 130:12 145:12,14 147:11</p> <p>1-(800) 154:4</p> <p>1,000 59:3 60:1,19 61:2,6,16 74:4 77:2 145:13</p> <p>1,500 59:19</p> <p>1,700 61:13</p> <p>1,800 60:14</p> <p>1.02 99:8</p> <p>1.6 39:18</p> <p>1.8 71:1</p> <p>1:00 190:1</p> <p>10 18:7 36:17 69:14,16 133:5</p> <p>10,000 145:14,15</p> <p>10:00 92:1</p> <p>100 60:11,17 61:2,11,12,15 74:3 170:4 182:17</p> <p>108 5:13</p> <p>10903 1:15</p> <p>11 90:6,8 133:5</p> <p>12 23:16 39:10 133:5</p> <p>12:01 190:9</p> <p>123 5:17</p>	<p>12-fold 59:14</p> <p>13 98:14</p> <p>130 5:18</p> <p>15 7:22 61:1 118:19 119:8 181:7</p> <p>15,451 98:17</p> <p>150 59:11</p> <p>1503 1:16</p> <p>16,300 98:10</p> <p>16,589 98:16</p> <p>18 162:21 163:1</p> <p>18,500 98:2</p> <p>187 5:19</p> <p>19 4:9</p> <p>1950s 188:13 189:8</p> <p>1960s 171:22</p> <p>1989 97:21 98:22</p> <p>1997 49:14 60:15 74:19 84:5 88:13 133:6</p> <hr/> <p style="text-align: center;">2</p> <p>2 60:18 61:14,15 72:3 78:17 90:8 165:8</p> <p>2.1 71:21</p> <p>2.24 71:7</p> <p>2.3 72:3</p> <p>2.5 99:4</p> <p>2.6 98:20</p> <p>2.7 56:17</p> <p>2.72 99:1</p> <p>2.9 98:18 99:3</p> <p>20 18:7 36:18</p>	<p>39:15 52:13 60:18 73:8 161:10</p> <p>200 60:12 61:1 99:14</p> <p>2001 70:13</p> <p>2002 10:16 28:14 35:10 112:6</p> <p>2003 98:22</p> <p>2005 112:2,10 122:7</p> <p>2007 11:12 28:19 35:11 72:1</p> <p>2008 29:1</p> <p>200-fold 61:7</p> <p>2011 122:8</p> <p>2012 38:1 90:5</p> <p>2013 37:12 98:1,9</p> <p>2014 1:12 7:19 29:10 32:9</p> <p>20-fold 59:8,16 66:16,21</p> <p>21 39:16 118:17</p> <p>22 38:11 39:2</p> <p>23 98:8</p> <p>23.4 39:17</p> <p>25 97:22 180:21</p> <p>250 147:11</p> <p>26 4:11</p> <p>28 1:12 75:5</p> <hr/> <p style="text-align: center;">3</p> <p>3 17:1 39:19 60:3 85:3 90:8 145:15 183:3</p> <p>3.2 98:20</p>	<p>3.3 99:4</p> <p>3.9 61:5</p> <p>3:20 8:2</p> <p>30 7:16 97:14 145:5 146:8 149:13 161:10 182:11</p> <p>300 60:2</p> <p>30s 184:22</p> <p>30th 7:19</p> <p>31 1:16 4:13,14</p> <p>32 39:13</p> <p>33 184:22</p> <p>34 184:22</p> <p>345 122:12</p> <p>353 56:9</p> <p>36 39:19</p> <p>38 36:5 97:11 98:7</p> <p>39 36:17</p> <hr/> <p style="text-align: center;">4</p> <p>4 17:1</p> <p>40 71:4 72:21</p> <p>41 36:16</p> <p>42 4:16</p> <p>43 4:17,19</p> <p>44 5:2</p> <p>445 98:17</p> <p>450 59:13</p> <p>48 98:11</p> <p>49 122:10</p> <hr/> <p style="text-align: center;">5</p> <p>5 36:16 85:3,10</p> <p>50 10:8 69:16 90:7</p>
--	--	--	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 2

<p>150:12 180:22</p> <p>500 89:2</p> <p>52,000 46:20</p> <p>52.7 39:18</p> <p>528 122:10,12</p> <p>544 79:11</p> <p>577 122:8</p> <p>59 32:10 38:9 39:2,13</p> <hr/> <p style="text-align: center;">6</p> <hr/> <p>6 4:2 23:17</p> <p>6/581 56:11</p> <p>600 78:14</p> <p>60s 188:13 189:8</p> <p>67 5:6 98:3 122:13 129:19 130:7</p> <hr/> <p style="text-align: center;">7</p> <hr/> <p>7,000 56:9</p> <p>70 130:7</p> <p>700 85:18</p> <p>71 39:6</p> <hr/> <p style="text-align: center;">8</p> <hr/> <p>8 4:6 97:14 122:11</p> <p>8:07 1:12</p> <p>80 78:16</p> <p>875 78:18</p> <hr/> <p style="text-align: center;">9</p> <hr/> <p>9 98:5</p> <p>9,000 79:9</p> <p>9.3 35:4</p> <p>9:45 8:1</p> <p>92 5:9</p>	<p>95 98:19 99:3</p> <hr/> <p style="text-align: center;">A</p> <hr/> <p>a.m 1:12</p> <p>abandoning 15:1</p> <p>ability 13:3 30:22 31:22 192:4</p> <p>able 7:8 26:3,4 79:4 145:6 146:8 150:8 155:1 160:10 164:3,4 167:15,18</p> <p>abnormalities 71:9 72:6,9 79:15 82:11</p> <p>abortion 56:4,7 118:16 119:16 150:5</p> <p>abortions 58:2,11</p> <p>Abou-Ali 2:19 5:14 20:14,15 108:8,11,14 125:6 126:19 127:4 129:22</p> <p>absence 180:1</p> <p>absent 9:15</p> <p>absolutely 128:9 133:3</p> <p>academia 104:22</p> <p>academic 110:14</p> <p>accept 164:3</p> <p>accepting 64:12</p> <p>accessibility 108:3</p> <p>accident 10:10</p> <p>accidental 141:14</p> <p>accidentally 154:4</p> <p>accommodate</p>	<p>7:10</p> <p>according 110:10,22 111:8 113:1 118:17 119:15</p> <p>accordingly 120:13</p> <p>account 56:14 57:11</p> <p>accrual 30:5</p> <p>accumulate 149:13</p> <p>accumulated 61:18 99:12</p> <p>accuracy 35:1</p> <p>Accutane 146:1 153:21 154:1,14 165:1</p> <p>Accutanes 164:20</p> <p>achieved 33:10 39:4 107:11</p> <p>acid 55:13 165:2</p> <p>acknowledge 100:14</p> <p>ACOG 147:17</p> <p>across 31:9,10 106:11 132:9 140:12</p> <p>act 28:20 113:3 120:12 123:3</p> <p>Acting 23:11</p> <p>action 191:11,16 192:6,7</p> <p>active 71:19 112:22 121:19 137:5</p> <p>actively 148:8</p> <p>activities 22:19</p>	<p>42:13 105:14 126:2 171:18 176:3</p> <p>activity 8:21 13:22</p> <p>actual 68:15 73:9</p> <p>actually 9:1 12:16 13:9 17:10 18:12 19:6,15 24:12 25:5 42:17 64:10,11 72:11 73:12 76:16 84:12 107:11 120:10 124:20 129:3 132:6 138:8 139:6 154:6 187:6</p> <p>Adacel 121:20 122:5</p> <p>adalimumab 38:14</p> <p>add 40:20 77:10,13 150:17 151:17 163:6 187:19</p> <p>added 38:7</p> <p>Adding 149:8</p> <p>addition 25:3 99:9 109:16 112:1 116:16 117:5</p> <p>additional 151:17 160:6</p> <p>Additionally 124:6</p> <p>address 13:3 92:8 105:18,21 115:1 129:19 153:17 157:3 176:21 177:7 180:1 183:13 185:21</p> <p>addressed 141:2</p>
---	--	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 3

<p>157:5</p> <p>addresses 106:9</p> <p>addressing 19:1</p> <p>Adel 2:19 5:14 20:15 108:8</p> <p>adenovirus 95:16,18</p> <p>adhere 102:20</p> <p>adherence 106:2</p> <p>administered 32:2</p> <p>administration 1:2 94:22 118:8</p> <p>admit 108:21</p> <p>ado 19:2</p> <p>adopt 102:19</p> <p>Adrian 2:20 20:8 89:11 127:22 138:18 182:1</p> <p>advance 7:9 24:9 154:16</p> <p>advancing 17:12</p> <p>advantage 14:2 124:6 151:3 184:14</p> <p>advantageous 101:15</p> <p>advantages 62:5,21 93:20 100:20 101:1 102:1,11 130:22 150:1,20 151:6,18 165:9 186:3</p> <p>advent 137:17</p> <p>adverse 117:11 118:15 119:7 123:4 124:13 126:4 128:22</p>	<p>157:18,22 158:10 164:15</p> <p>advertisement 175:4</p> <p>advertisements 147:19</p> <p>advertising 64:18 184:12</p> <p>advice 26:10 65:19 86:12 148:20</p> <p>advise 69:8</p> <p>adviser 23:3 44:15</p> <p>advisers 85:2 88:16</p> <p>advising 135:15</p> <p>Advisor 4:21</p> <p>advisors 105:1,11</p> <p>advisory 84:3 87:1 99:22 101:11 104:21 107:19 129:6 183:12</p> <p>advocacy 115:19</p> <p>advocates 81:22</p> <p>AED 21:11 132:8 147:4 155:19 158:14 166:8 184:11</p> <p>affect 30:7 40:20 51:3 163:10 189:4</p> <p>affected 60:1 145:16</p> <p>affects 121:13</p> <p>African 74:3</p> <p>afternoon 8:2 16:19 26:5 65:15 153:17</p> <p>against 136:1</p>	<p>170:2</p> <p>age 12:3 48:15 55:6 58:3 93:8 95:6,20 118:10 120:4 163:9 173:5</p> <p>agencies 14:13 28:10 103:10 111:20 127:10</p> <p>agency 23:17 24:3 28:16,20 29:12 30:1 110:6 112:9 119:1,3</p> <p>Agendas 7:1</p> <p>agents 178:20</p> <p>ages 179:14</p> <p>aggregate 99:10 100:1 107:8,18</p> <p>aggressive 147:8</p> <p>ago 23:17 24:8 69:14 71:12 137:9 168:4 178:18</p> <p>agonize 87:1</p> <p>agreeing 166:17</p> <p>agreement 102:17</p> <p>agreements 68:7</p> <p>ahead 19:22 42:4 64:3 78:9 85:21 91:15</p> <p>AHRQ 24:11</p> <p>aim 52:12</p> <p>aims 113:21</p> <p>alarms 46:6 66:13</p> <p>Albano 2:3 5:10 21:12,13 92:13,16 107:13 175:21 186:18</p>	<p>alcohol 81:5</p> <p>alert 141:16,18,20</p> <p>Alison 26:3</p> <p>Allen 2:16 24:21 45:4 142:20 144:2 153:20 154:5 165:13 177:8</p> <p>alleviate 106:5</p> <p>allotting 14:7</p> <p>allow 19:20 150:21 151:1</p> <p>allowed 128:7</p> <p>allowing 181:20</p> <p>allows 60:3</p> <p>alluded 125:5</p> <p>alone 97:17</p> <p>already 7:1 49:6 53:5 55:20 92:21 97:10 104:1 108:1 114:13 135:8 169:18 181:5 187:1</p> <p>alternative 13:21 14:8,22 16:3 17:3 39:20 110:16 126:6 156:21</p> <p>Alternatively 7:11</p> <p>alternatives 152:22 186:5</p> <p>altruistic 153:11</p> <p>am 19:2,11,17 20:8,10,20 21:4,9,10,12,13, 16 22:7,8,11,12,13, 15,16,21 23:2,3,6,7,9,10,1</p>
--	--	--	--

Capital Reporting Company
 Food and Drug Administration Public Meeting 05-28-2014

Page 4

<p>3,14 24:2,4,18,20 25:9,12,13,15 31:16 44:18,21 47:22 49:6,10 50:16,18 51:7 60:7 65:13 67:20 69:11 92:16 104:13 126:15 153:13,16 165:21 166:5 171:13 182:11 183:11 191:9,12 192:5,6</p> <p>Amendments 28:20</p> <p>America 60:8 127:13</p> <p>American 5:7 21:11 49:9 55:3 74:3 84:1 97:8,11 132:8 147:4 155:18 158:14 166:8 181:6 184:11</p> <p>amniocentesis 50:14</p> <p>among 17:13 30:13 41:21 45:12 56:10 68:19 76:2,3 81:22 90:7 94:10 98:6,16 99:2,15,20 128:14</p> <p>amount 6:17</p> <p>Ana 25:11</p> <p>analyses 4:18 35:3 43:14 83:7 103:17 107:22</p> <p>analysis 12:19 16:15 31:19 33:3</p>	<p>34:11,22 35:3 36:3 49:3 58:17 76:22 77:1 81:15 99:13 101:17 104:8 105:9 107:8,14 108:1 112:17 119:11 120:8 132:20</p> <p>analytical 101:13</p> <p>analytically 102:14</p> <p>analyze 58:1,4 107:17 119:12</p> <p>analyzed 32:14 71:13 99:11,16</p> <p>and/or 129:8</p> <p>Andrade 2:4 21:22 22:1</p> <p>animal 11:15 45:11</p> <p>announcement 7:15 91:17 114:19,21 115:5</p> <p>annual 100:2</p> <p>anomalies 77:7 118:17 119:19 171:21</p> <p>answer 52:5 66:2 84:15 122:22 128:1 131:21 177:9</p> <p>answering 165:21</p> <p>answers 148:14</p> <p>anthrax 25:17</p> <p>anticipate 131:3</p> <p>anticipating 127:1 153:16</p> <p>anticonvulsant 50:6 70:16 81:15</p>	<p>158:16</p> <p>anticonvulsants 49:18 50:4 55:12 56:9 57:7 159:10 184:21</p> <p>anticonvulsants/ anti-epileptic 49:16 55:8</p> <p>Anti-Epileptic 5:7 44:16 49:9 55:3 84:1 90:13 97:8 181:6 185:3</p> <p>antiretroviral 37:1 38:4,20 97:19 99:10 100:6 104:18</p> <p>antiretrovirals 185:4</p> <p>Antiviral 97:9</p> <p>anxiety 178:13</p> <p>anxious 178:11</p> <p>anybody 64:3 66:15 73:1 85:22 131:11 140:19 142:8 148:20</p> <p>anymore 137:22</p> <p>anyone 42:2 165:20</p> <p>anything 88:10 129:13 143:6,7 148:4 176:5 177:11 180:4</p> <p>anywhere 149:1 177:11</p> <p>apart 164:11</p> <p>apparent 65:21 100:7 148:5</p> <p>appeared 90:5</p>	<p>Appearing 3:13</p> <p>appears 176:21 191:4</p> <p>Applause 64:1 83:18 106:21 123:10</p> <p>applicable 155:4</p> <p>application 125:19 126:3 174:6</p> <p>applications 125:20 129:17</p> <p>apply 122:18 127:15</p> <p>applying 173:22</p> <p>appreciated 6:14</p> <p>approach 28:15 71:2 111:16 185:22</p> <p>approaches 1:4 6:10 9:9 13:18 14:22 16:4 17:3,11 39:20 104:7 126:11 156:22 180:4</p> <p>appropriate 28:3 93:19 95:2 96:2,6,22 104:22 106:14 140:15 176:2 183:9</p> <p>appropriately 103:1</p> <p>appropriateness 171:10</p> <p>approval 5:11 9:14 27:18 29:21 123:18</p> <p>approvals 97:4 105:5</p> <p>approve 127:11</p>
--	--	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

<p>approved 9:22 30:11 33:21 34:17 35:20 36:12 37:10,21 38:7 93:3 95:2,6</p> <p>approximately 7:16 97:11,14 98:11</p> <p>APR 97:13 98:20 99:13 100:12,13 107:13</p> <p>Arbor 132:15</p> <p>arc 178:14</p> <p>area 7:21 9:4 15:18 18:16 70:17 102:19 122:20 132:15 162:18 187:4 189:20</p> <p>areas 14:9 106:11 128:15 132:16</p> <p>arena 108:22 109:15 112:8 113:3</p> <p>aren't 143:20 149:18 179:6</p> <p>argue 54:16 76:10 145:8 163:17 164:17</p> <p>Army 21:17,18</p> <p>arrives 9:2</p> <p>articles 34:19</p> <p>ascertain 32:19</p> <p>ascertained 133:9 173:13</p> <p>ascertainment 171:21 172:6,17</p> <p>ascertains 173:4</p>	<p>aside 92:8</p> <p>aspect 145:21</p> <p>aspects 44:22 45:2 103:7 166:4</p> <p>aspirin 143:12</p> <p>assess 30:22 32:1 40:15,19 146:21</p> <p>assessing 16:4</p> <p>assessment 24:4 102:8 168:20,22</p> <p>assigned 51:2</p> <p>assist 141:12 142:14</p> <p>assistant 68:22</p> <p>assistants 82:16 136:12</p> <p>Associate 4:10 5:4 23:20</p> <p>associated 33:2 74:5 90:9 149:22 159:11,14</p> <p>association 65:22</p> <p>assume 160:17</p> <p>assurance 34:21</p> <p>assure 164:19</p> <p>Atlanta 71:20 171:7,14 172:18,20</p> <p>atrial 75:13 80:2</p> <p>attempt 13:6</p> <p>attendance 6:13</p> <p>attention 41:22 57:15 63:16 70:19 166:11</p> <p>attorney 191:13</p> <p>audio 192:3</p>	<p>Australia 21:8</p> <p>Australian 90:13</p> <p>author 90:4</p> <p>authorities 117:7</p> <p>authority 11:13 12:5 28:21</p> <p>autism 164:1</p> <p>Autoimmune 38:16</p> <p>automated 47:10</p> <p>Ava 2:7 25:6 189:13</p> <p>available 7:2,16 8:4 39:13 102:8 109:1 177:4</p> <p>Avenue 1:15</p> <p>avoid 9:20 101:2 113:9</p> <p>aware 148:7 163:10 174:13</p> <p>awareness 30:11 101:22 176:3,6,19 177:5</p> <p>away 66:15 76:17 80:1 91:8 148:12 170:13,22</p> <p style="text-align: center;">B</p> <p>babies 73:1,2</p> <p>baby 136:1,3,4,8 140:5 177:12</p> <p>background 27:2 109:7 128:21 151:9 161:11</p> <p>backgrounds 109:8</p> <p>balance 76:14 105:17</p>	<p>balances 77:17</p> <p>ballpark 142:16</p> <p>bar 167:14</p> <p>bark 43:8</p> <p>barriers 93:22</p> <p>base 89:3</p> <p>based 11:15 32:3 36:22 37:1,3,5,7 38:14,18,19,21 88:11 94:3 134:16 142:8 160:15,17 165:8,13 172:17 185:13</p> <p>baseline 77:11,12,14</p> <p>basic 188:11</p> <p>basically 111:19 113:16 121:10,11 128:19 166:22 180:5</p> <p>basis 17:10 72:18 77:19 82:18 89:19,22 100:2 112:13</p> <p>bear 76:19</p> <p>became 88:18 148:5 155:2</p> <p>become 16:2 74:19 75:22 97:22 146:2 188:22</p> <p>becomes 150:7 187:8</p> <p>begin 6:19 89:5 92:6,20 148:3</p> <p>beginning 61:14 69:6 84:21 88:22 98:14 112:20</p>
---	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 6

<p>147:5 148:10,18 170:8</p> <p>begun 131:1</p> <p>behalf 6:8 8:19</p> <p>believe 48:16 52:20</p> <p>benefit 105:12 131:15 174:14 183:5</p> <p>benefits 105:22 152:21</p> <p>Berliner 2:5 24:2 64:5 152:2</p> <p>besides 117:2 118:19 120:6</p> <p>best 15:16 106:9 116:22 124:21 152:13,15 169:22 170:1,12 179:13 181:18 192:3</p> <p>better 14:3 18:22 31:5 141:3 157:3,10 159:20 162:7 170:19 182:9 184:16,17</p> <p>beyond 13:21 14:8 17:14 18:6</p> <p>bias 62:8</p> <p>biases 113:10</p> <p>bibliographic 34:5</p> <p>bifida 89:7</p> <p>biggest 88:19 178:21</p> <p>biologic 94:4,19</p> <p>biological 1:5 6:11 9:10 72:7 120:5</p> <p>biologically 73:5</p>	<p>biologics 27:19 28:7 36:7</p> <p>birth 13:8 20:21,22 25:1,14,22 30:15 40:4 46:18 47:9,20 51:5 52:19 54:11 55:1 57:3 58:15,21 59:1,8 60:4 63:18 70:2,3 71:20,22 72:7,14 73:6 74:14 75:9,11 76:9 78:17 81:8 98:18,22 99:3 101:12 119:18 129:8 133:4 134:4 144:12 149:19 150:3 157:22 158:1 162:8 164:13,18 167:22 168:1,5 169:3 171:7,13,17 172:7,9 174:1 181:18</p> <p>birthmarks 77:6</p> <p>births 60:1 77:3 98:17</p> <p>bit 10:13 43:7 44:2 49:12 51:19 55:17 60:15,22 64:3,5,9 66:22 97:10 125:3 126:17 130:20 147:7 153:16 156:3 158:6 167:14 181:19 182:8 187:7</p> <p>Blackberries 6:21</p> <p>blessed 167:6</p>	<p>block 176:4</p> <p>Board 101:12 104:21</p> <p>booths 115:19</p> <p>boring 70:20</p> <p>born 70:15,21 74:22 136:4,8</p> <p>boss 19:12</p> <p>Boston 25:1 49:14 70:17 87:10 147:10</p> <p>bottom 38:5 73:1</p> <p>bought 81:6</p> <p>bound 76:20</p> <p>Branch 26:1 171:13</p> <p>brand 94:22 95:14 118:8 187:1</p> <p>branding 120:22</p> <p>break 8:1 90:19 91:15 189:16,17</p> <p>breaking 158:5 189:22</p> <p>breaks 8:5</p> <p>breast 96:17</p> <p>brief 44:19 179:11</p> <p>briefly 49:11 62:4</p> <p>Brigham 71:4 77:3</p> <p>bring 157:18</p> <p>bringing 6:17 65:14</p> <p>broad 106:17 171:21</p> <p>broadening 183:19</p> <p>broader 150:6</p>	<p>broadly 32:5</p> <p>brought 92:22 124:11 140:16 164:21</p> <p>bucket 159:15 163:8</p> <p>budget 87:18 105:5</p> <p>budgets 101:7,10</p> <p>buffet 91:18</p> <p>Building 1:16</p> <p>bunch 24:7</p> <p>bupropion 37:1,2,19</p> <p>burden 102:5</p> <p>business 105:16,17 106:2</p> <p>busy 137:21</p> <p>button 20:3</p> <p style="text-align: center;">C</p> <hr/> <p>Caitlin 69:13</p> <p>calculate 120:9</p> <p>calculated 39:16</p> <p>calculation 59:6,21,22 60:3 78:13 121:13</p> <p>California 22:7 25:11</p> <p>campus 1:15 25:5</p> <p>Canada 20:16 68:20 128:6 134:10</p> <p>cancer 96:17 178:21 179:5</p> <p>canvass 130:19</p> <p>Capital 1:20</p>
---	---	---	---

Capital Reporting Company
 Food and Drug Administration Public Meeting 05-28-2014

Page 7

<p>capture 43:3</p> <p>capturing 157:22</p> <p>carbamazepine 81:9</p> <p>cardiacs 59:4</p> <p>cards 64:19</p> <p>care 14:13 22:2 28:10 30:12 48:4 93:13 101:5,21 102:5 110:17 114:15 115:2 116:2,7,8,17 117:19 120:21 121:3,5 125:16,17 132:11 147:20 172:9,15 175:16 182:6,7,12</p> <p>careful 132:21 140:7 163:15 165:4</p> <p>carried 70:12</p> <p>case 40:2,3 46:3,4,15 47:16,19 52:18 54:21 57:21 66:10 78:3 101:16 104:5 118:4 133:2,20 138:17 153:2 173:22 174:7,8 179:1,11 182:22</p> <p>cases 42:13 61:9,15 76:16 98:2,17 99:14 100:1,15 114:6 115:3,15 116:2,3,15 117:3,6,11,12,16 119:5 120:1 121:8 124:18 139:12 155:19</p>	<p>179:13</p> <p>categories 29:5 129:13</p> <p>Caucasian 74:4</p> <p>cause 100:9 109:20 188:16</p> <p>caused 188:20</p> <p>causing 161:1</p> <p>caution 18:8</p> <p>CBER 23:12 31:10</p> <p>CBRD 110:17</p> <p>CDC 20:22 30:16 84:8 124:7 168:2 171:13</p> <p>CDC-based 47:21</p> <p>CDER 4:5,8,10,13,15,2 1 8:19 19:7 23:4,16 26:16 31:9</p> <p>cell 6:21</p> <p>cell-free 132:18</p> <p>center 1:16 4:5 6:5 20:21 21:5,18 22:22 24:22 25:13 47:20 105:7 107:15 132:14</p> <p>Centers 25:22</p> <p>central 138:12 172:18 179:3,7</p> <p>centralized 102:3</p> <p>certain 80:3 110:11 118:14 143:5 151:9 157:3 164:4 169:17 173:1,2</p> <p>certainly 65:3</p>	<p>76:12 104:5 144:20 145:15 158:11 172:22 186:22 189:21</p> <p>certainty 32:20</p> <p>certificate 13:8 191:1 192:1</p> <p>certify 119:15,16,18 191:3 192:2</p> <p>cetera 40:19 50:6,15 89:7 124:13 170:19 172:2</p> <p>challenge 43:2 79:13 81:18 121:8 122:15 128:15 140:14 141:1 147:6 157:21 158:17 161:6 164:2 180:9</p> <p>challenges 15:8 93:20 100:20 102:12 120:14 121:4,14 122:3 125:3 126:8,14 127:10 128:1,13 129:2 131:1,5 160:12 165:9,11</p> <p>challenging 108:22 109:4 126:8,16 127:1</p> <p>Chambers 2:6 22:6 131:18 140:10 149:8 161:13 176:9 185:2 187:19</p> <p>chance 19:19 88:7 184:16,17</p> <p>chances 148:21</p>	<p>change 29:2 33:5 36:20 57:4,10 88:10 133:7 137:7</p> <p>changed 11:12</p> <p>changes 28:21 34:1,16 56:21 78:16,19 134:3 136:4</p> <p>changing 58:12 133:4 140:10</p> <p>chapter 24:13 26:11</p> <p>character 182:18</p> <p>characteristics 31:2 34:13 35:6 41:10 97:6 173:3</p> <p>chasing 180:12</p> <p>check 6:22 190:6</p> <p>checked 7:6</p> <p>checks 34:21 88:16</p> <p>cheerleaders 148:6,10</p> <p>chemical 11:15</p> <p>chemotherapeutic 178:20</p> <p>Chicago-Ann 132:15</p> <p>child 73:15 118:2 134:18 159:2 172:13</p> <p>childbearing 48:15</p> <p>children 45:10 70:11,17,21 75:2 158:16,19 160:5,7 172:7</p>
---	--	--	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 8

<p>child's 159:1 chips 136:20 choice 104:15 179:20 choose 165:18 chorionic 50:14 chose 32:2 35:7 126:12 CHRISTINA 2:6 chromosomal 171:20 chromosome 71:9 72:9 chronic 11:21 cigarette 81:3 cited 73:6 claims 40:3 47:10 clairvoyant 140:21 clarifying 4:16 5:17 42:5 64:4 67:9 83:19 89:12 106:22 123:13 class 11:15 95:3 96:3 99:10 103:19 111:1,6 175:2 classic 178:9 classification 110:12 classifications 110:11 classified 75:13 110:22 111:8 clean 170:11 clear 105:13 186:19 187:3 clearance 37:14</p>	<p>clearly 8:12 144:17 170:12 cleft 61:1 78:20 155:19 clefts 59:5 60:18 85:20 89:6 clinical 4:21 11:16 23:3 27:17 32:22 33:12,20 34:8 37:18 38:13 41:3 45:14,20 48:4 68:5,9 102:2 177:15 clinically 31:3 151:11 clinician 65:6 clinicians 64:20 100:15 117:16 177:16 clinics 172:11 clock 136:9 close 27:15 55:22 59:9 closed 39:8,10 118:4 157:7 closely 43:20 124:7 closer 59:17 closing 183:2 clue 143:21 clues 46:6 cluster 185:12 CMS 174:16 Coast 132:12 Coast-West 132:12 Code 118:18</p>	<p>coder 75:11 codes 75:10 coffee 7:22 8:3 cognitive 158:15 coherent 102:8 cohort 40:2 46:15,16,19 48:2 53:16 59:13 70:12 113:4 cohorts 47:3 62:12 COL 2:8 21:16 141:9 174:12 colds 143:6 collaborate 17:16 186:13 collaboration 30:13,16 102:17 125:1 collaborations 159:19 collaborative 18:19 46:18,20 104:11,12 colleagues 86:19 87:9 158:17 189:11 collect 9:16 41:16 112:16 113:21 116:18 125:11,16 168:18,19 173:8 177:20 collected 10:3 11:2 33:7 62:9 93:2 118:4 119:12,14,21 120:19 collecting 28:1,4,6 60:14 107:16</p>	<p>143:17 collection 4:18 11:3 16:15 27:4,20 28:13,15 29:6 41:20 43:14,22 44:5 101:16 104:7 105:8 108:10 109:5 117:10 Collection/ Experience 5:13 108:12 collections 157:9 collectively 12:13 collects 117:20 171:19 combination 97:1,14 combine 47:14 combined 96:7 comes 104:6 118:12 139:22 162:1 comfortable 88:18 coming 23:17 47:10 84:12 168:6 185:16 comment 7:4 16:19 17:4 42:22 65:10 74:16 91:7 137:1 152:2 157:16 171:9 174:13 176:10,12 188:11 190:2 comments 7:12,18 20:6 27:15 29:14 58:20 68:12 88:8 123:11 146:22 147:3 155:17</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 9

<p>165:14 189:12</p> <p>commitment 29:20 35:17 103:14,15 185:17</p> <p>commitments 105:19</p> <p>committee 6:8 84:4 87:1 99:22 100:16,18 104:20 107:19 129:6 183:12</p> <p>common 29:18 59:4 62:14 65:4 73:6 74:2,4,20 75:4 76:1 79:16 80:1 89:9 94:8 100:9 102:19 111:3,10 113:3 115:4 116:6 147:12 161:15 163:19</p> <p>commonly 39:9 47:2,18 60:16 149:11 171:8,16</p> <p>communicate 66:11,15 67:1 89:13,19,22 90:2 176:15 178:1</p> <p>communicated 89:21 187:22</p> <p>communicating 89:14,16</p> <p>communication 15:17 16:21 32:21 66:5,12 89:12 102:21,22 140:12</p> <p>communications 34:3,4 103:9 115:15</p>	<p>companies 37:15 56:6 78:2 89:4 100:13 101:6 102:18 103:2,11 107:10 110:13 111:16 113:20 114:19 115:7 122:19 124:18 135:15 184:2,4,15 186:13</p> <p>company 1:20 72:13 88:1 96:2 111:19 115:6 116:12 117:1,12,13</p> <p>company-sponsored 116:20 117:5</p> <p>comparable 58:14 63:5,9</p> <p>comparative 150:21</p> <p>comparator 11:7 90:22 171:11 172:3 173:17</p> <p>compare 11:8 48:10 56:15 60:19 103:19 151:1</p> <p>compared 67:17 95:9 99:5,19</p> <p>comparison 5:6 50:18 63:8 67:11,14,21 68:15,16 69:11,12,18 72:18 76:12 77:16,19 78:15 79:10 80:7,14 82:21 83:15 91:5,9,10 98:21</p>	<p>104:1 129:1 150:8 159:1 166:19 167:13 171:9</p> <p>comparisons 97:4 173:15</p> <p>compelling 146:14</p> <p>competing 102:18</p> <p>competition 101:20 103:2</p> <p>complaints 70:2</p> <p>complement 15:3 144:8</p> <p>complementary 14:22 41:17 97:13</p> <p>complete 71:13 139:2 181:16</p> <p>completed 39:10</p> <p>completely 137:3</p> <p>completeness 35:1 120:18</p> <p>complex 96:18 97:1 100:20 102:14 104:11</p> <p>complexity 100:21 102:13</p> <p>complicated 151:20 161:15 170:20 183:22 184:7 186:15 189:1</p> <p>complications 129:8 186:19</p> <p>complied 175:8</p> <p>component 83:15 95:15</p> <p>comprehensive</p>	<p>32:7 40:14 100:4 102:7</p> <p>comprised 104:20</p> <p>computer-assisted 69:1</p> <p>computerized 47:12</p> <p>concentrating 62:10</p> <p>concept 127:16</p> <p>conception 54:9 120:4</p> <p>concern 10:20 30:1 62:7 90:2 93:6 96:7 99:15 135:12 137:9 163:20 164:15</p> <p>concerned 8:21 15:19 51:6 89:17 135:4 137:22</p> <p>concerning 175:2</p> <p>concerns 163:18</p> <p>concluded 190:10</p> <p>conclusion 106:12</p> <p>conclusions 41:9 62:3</p> <p>concomitant 96:6 179:16</p> <p>concurrent 146:14</p> <p>condition 57:9 94:8 96:12 139:1 164:22 172:15 173:1</p> <p>conditions 9:19 11:21 12:5 72:10 152:20 171:20</p> <p>conduct 15:9 20:22 21:14</p>
---	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 10

<p>28:18 30:14 40:18 41:6 64:21 108:5 112:17 114:8 116:22 169:16</p> <p>conducted 12:6 27:8 30:21 33:17 34:9,22 39:22 48:13 71:4 127:12</p> <p>conducting 16:2 60:20 168:5</p> <p>conducts 107:13</p> <p>conference 1:16 7:21</p> <p>confidence 57:13 61:17,19 66:8 98:19 99:4 150:15</p> <p>Confidentiality 103:6</p> <p>confirm 135:2</p> <p>confirmation 121:1</p> <p>confounder 144:7,18</p> <p>confounders 104:2</p> <p>confounding 97:5 151:9 188:19</p> <p>congenital 71:20 118:17 119:18 171:7,15 189:6</p> <p>Conlin 2:7 25:7,9,12 136:22 137:2 189:13</p> <p>connection 158:8</p> <p>consecutive 77:2</p> <p>consensus 100:3</p>	<p>consent 49:20</p> <p>consequences 179:8</p> <p>consider 58:12 68:1 75:16 88:9 105:16 114:10 119:21,22 151:21</p> <p>considerations 37:18 93:21 101:14 104:3</p> <p>considered 29:14 32:5 33:1 39:10 81:10 118:15 176:2</p> <p>considering 56:13 57:6 83:13 125:8 130:8 175:2</p> <p>considers 50:9</p> <p>consist 37:17</p> <p>consistency 106:11</p> <p>consistent 70:19 102:9 154:19</p> <p>consisting 36:6</p> <p>consolidated 101:22</p> <p>constant 84:4 136:21 176:22</p> <p>constitute 84:10</p> <p>consultation 106:14</p> <p>consulted 44:14</p> <p>consumer 180:6</p> <p>consumers 116:17</p> <p>Cont 3:2 5:1</p> <p>contact 121:5 136:3 137:18 138:3,5 181:14</p>	<p>182:14</p> <p>contacting 182:4</p> <p>contain 115:1</p> <p>contained 32:13</p> <p>Containing 37:7</p> <p>content 29:3 144:1</p> <p>contentious 75:18</p> <p>context 12:20 103:11 124:14 155:6,14 156:20 157:1</p> <p>continue 61:3 79:4 88:20 89:1 135:13</p> <p>continued 69:17</p> <p>continues 79:7 177:4</p> <p>continuing 89:5 152:21 156:10</p> <p>continuously 161:17</p> <p>contraception 52:7</p> <p>contradictory 152:4</p> <p>contrast 95:16</p> <p>contribute 40:17 152:8</p> <p>contributed 36:20 38:13 39:22 41:2,13</p> <p>contributions 100:16</p> <p>contributors 82:14</p> <p>control 25:22 40:2 46:16 47:16,19 63:7 121:14 128:16</p>	<p>146:15,16 150:18 151:3</p> <p>controls 79:13 150:16 151:22</p> <p>convenient 171:16</p> <p>conversation 152:16 153:2 158:3 165:7 185:19</p> <p>coordinating 105:6 107:15</p> <p>coordination 168:14</p> <p>copies 83:2 124:2 134:11</p> <p>core 34:22</p> <p>correlation 188:14</p> <p>cost 63:11 105:22 147:7</p> <p>Coster 2:8 21:16 141:9 174:12</p> <p>costs 146:2</p> <p>counsel 191:10,13 192:5</p> <p>count 76:10</p> <p>counties 172:18</p> <p>countries 35:22 98:3 110:19,20</p> <p>country 132:15,16</p> <p>country-specific 111:9,11</p> <p>counts 34:14 82:19</p> <p>couple 155:20</p> <p>coupon 154:19</p> <p>course 28:11 51:12 58:8 61:21 74:11 78:21 83:6 85:7</p>
--	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 11

<p>126:7 128:15 165:6 COURT 191:1 courtesy 124:2 covariance 11:4 coverage 24:5,6 CPRD 47:12 Cragan 2:9 20:20 84:8 155:16 167:7 171:7,12 Craig 2:11 21:4 create 66:13 credible 189:5 criteria 42:9,18 68:14 70:8,9 71:17 74:21 75:16 118:14 166:12 174:2,3 183:6 criterion 42:11 critical 106:15 128:9 161:21 185:15 crossed 19:14 crucial 68:14 184:13 C's 102:12 cumulative 61:5 100:4 179:15 current 4:12 15:6 26:19 27:5 29:16 31:22 44:4 102:10 123:6 130:10 146:11 188:8 currently 22:16 52:20 71:19 72:1 98:7 139:14</p>	<p>156:4 171:13 cut 146:17 cutting 135:7,10 _ <u>D</u> DABT 3:7 4:20 daily 105:7 Dana 2:20 20:7,8 89:11 127:22 138:18 182:1 dance 136:10 danger 177:21 dangerous 66:22 dark 55:9 data 4:18 5:13 9:12,15,21 10:2 11:3,16 13:7 14:1 15:10 16:8,15 17:10 18:4 27:4,19,20 28:2,4,6,13,15 29:5 31:4 32:9,18 33:11 34:11,15,22 35:1 36:19,22 37:2,3,5,8,11,18, 20,22 38:3,7,12,15,18, 20,22 39:12 40:4,16,21 41:2,12,16,20 43:14,22 44:5 47:10,19 51:15 55:2 56:4,7 60:7 61:17 71:5,13 93:9 100:5 101:16 102:8 104:7,9 105:3,8 107:11,16,17,20 108:9,12 109:5,11</p>	<p>112:16,17 113:21 116:18 117:9,21 118:7 119:11,12,14,20 120:18,19,22 123:20 125:17 128:9,12,19 135:22 141:17 156:22 157:9 161:8 165:19 168:17,19 170:11 171:19 177:20 180:2 database 21:21 40:3 117:14 118:20 119:1 databases 13:17 14:4 15:4 33:18 47:11 110:17 142:4,13,18 170:9 date 12:8 99:14 118:9,10 157:22 day 9:6 13:11,20 14:8 18:20 26:8 66:21 81:4 87:10 days 7:16 44:21 79:20 118:19 119:8 dealing 58:21 145:22 151:13 166:3 167:12 180:8 death 119:17 debate 75:19 134:19 debated 86:1 debating 86:15 December 37:12 decide 79:21 80:4</p>	<p>85:13 87:20 89:13 decided 175:1 deciding 82:19 decision 40:20 85:4,17,20 decision-making 78:8 decisions 93:12 183:4 decrease 137:14 146:11,12,20 decreased 137:12 defect 20:22 47:18,20 54:11 55:1 60:4 75:9,12,13 89:17 98:17,22 101:12 145:13 168:5 169:3 174:1 defects 20:21 25:1 26:1 30:15 46:18,22 47:9 51:5 52:19 53:18 57:4,15 58:16,21 59:8 63:18 70:3 71:20 73:7 74:14 78:18 79:18 80:2 81:8 89:6 98:18 99:3,7,20 100:8 129:9 133:5 134:4 144:12 145:7,8,11,12 149:19 156:7 161:5 162:8 164:13,18 167:22 168:1 171:8,13,15,17 172:7 173:4 174:6 defense 21:20</p>
--	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 12

<p>25:14 170:2 defer 165:22 define 138:12,15 163:16 defined 104:12 114:7 definitely 127:4 definition 48:1 52:14 70:6 119:6 132:1 138:10,11 163:1 174:1,7,8 degree 102:15 delay 148:2 delicate 136:10 delineate 93:21 delivery 54:13 128:11 147:11 150:5 172:19 181:16 demographic 50:4 118:6 demonstrate 93:18 denominator 121:12 denominators 121:9 Department 21:17,19 22:8 25:14 departments 172:10 dependent 113:17 121:11 160:1 depending 66:10 87:8 147:8 173:6 182:20 depends 52:5 70:6 111:19 118:13</p>	<p>149:6,10 depicts 104:17 deposition 191:5,8,12 depressed 178:11 deputy 5:14 9:1 DES 162:14,19 describe 31:2,12,21 34:7,12 36:2 110:8 described 30:6 112:10 114:18 185:7 188:13 describing 31:18 68:3 189:9 description 113:2 115:12 116:21 149:4 descriptive 34:11 deserved 130:11 design 5:2 15:9 28:19 44:9,11 93:15 104:7 106:7,14 112:15,19 140:14 166:12 183:9 designed 46:17 47:8,17 79:3 95:17 149:4 167:6 designing 166:16 designs 44:19,20 45:5 desirable 97:4 desire 69:2 desired 32:21</p>	<p>desk 7:7 91:21 190:5 despite 100:21 102:11 123:6 detailed 50:7 details 6:20 70:8,19 71:16 113:13 118:9 detect 124:3 detected 77:20 81:13 166:15 detecting 123:4 detection 114:2 122:21 160:18 162:5 determine 33:15,22 133:11 141:5 determined 76:20 160:15 determining 183:7 detriment 134:18 devastating 145:16 develop 41:6 74:21 developed 67:17 69:14 141:7 developing 174:22 development 22:12 24:7 40:6 63:14 158:2,15 161:22 163:5,11 170:15 developmental 20:21 158:18 159:14,20 develops 175:5 device 94:5</p>	<p>devices 6:21 130:6 diagnosability 134:4 diagnose 54:11,12 diagnosis 53:8,10,14,15 54:16 94:8 132:2,4 151:4 Diana 2:15 24:19 Diane 180:3 Diaz 23:20 44:9 109:8 186:2 didanosine 99:17 diddlies 77:5 diddly 73:3 Diego 22:7 25:11 differ 173:3 difference 57:14 182:3,11 differences 46:9 55:15 62:16 94:13 different 34:15 43:22 45:13,16 51:1,11,13 52:3 57:20,22 65:12 67:20 71:2,18 90:17 94:11,21 95:22 109:4 115:12 117:21 119:3 120:16 122:3 127:14 128:14 155:1 172:5 173:6 182:19,21 186:12 188:20 differentiate 93:17 differentiation 105:20</p>
---	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

<p>differently 138:15</p> <p>differing 128:5,14,22</p> <p>difficult 32:19 128:4,7 160:21 180:9</p> <p>diffuse 134:16</p> <p>dilemmas 147:9</p> <p>direct 103:9 129:10 172:3 173:15</p> <p>direction 191:8</p> <p>directives 106:10</p> <p>directly 180:14</p> <p>director 4:7,10 5:3,7,11,14 9:1 19:6 21:10,13 22:12,21 23:11 24:4,18,22 171:14</p> <p>direct-to-consumer 154:13</p> <p>disabilities 20:22 163:19</p> <p>disadvantages 62:5</p> <p>discernible 99:20</p> <p>disclosure 44:14</p> <p>discover 133:17</p> <p>discovery 103:8</p> <p>discuss 6:9 47:5 50:19 66:4 73:4 87:20 93:19 170:17</p> <p>discussed 13:19 28:4,5 41:18 85:1 107:4 137:3</p>	<p>discussing 94:15 171:2</p> <p>discussion 5:18 7:2 9:8 12:12 16:9,12,20 18:9,19 45:17 65:16 67:7 87:20 130:12,14,20 135:19 153:3 155:22 162:11</p> <p>discussions 17:6 18:2 155:22</p> <p>disease 25:22 30:9 35:13 94:2,7,12 96:12,21 97:5 111:2 129:14 149:10 185:12 186:5</p> <p>disease-based 32:11,15 40:10 93:18 96:19 100:22 150:18 183:8 185:5,21</p> <p>diseases 38:16 151:14</p> <p>dismiss 165:3</p> <p>dismissed 133:19 188:17</p> <p>disorders 71:10</p> <p>dissemination 104:9</p> <p>distinct 94:12 101:1</p> <p>distinction 94:1 138:20 139:9</p> <p>distribute 107:18</p> <p>distribution 55:11</p> <p>divide 135:1</p> <p>divided 60:11</p>	<p>61:10</p> <p>Division 23:11</p> <p>divisions 31:10</p> <p>DNA 132:18</p> <p>docket 1:9 7:12,18</p> <p>doctor 152:17</p> <p>doctors 64:7,11</p> <p>documented 43:6 87:2 103:1</p> <p>DOD 13:15</p> <p>dog 43:8</p> <p>dollars 87:16</p> <p>dominant/ recessive 71:10</p> <p>done 7:1 11:4 70:10 76:1,6 84:5 86:20 87:13 89:18 90:10,17 107:22 141:11 157:2 158:15 168:10 174:15,17 180:18 181:19</p> <p>door 170:14</p> <p>dose 110:1 174:21</p> <p>doses 94:21 179:15</p> <p>double 59:12,16</p> <p>Dr 8:15,18,22 12:17 19:9,11 20:7,14,20 21:3,9,12,22 22:6,11,20 23:2,9,13,19 24:2,15,21 25:3,6,9,18,19,2 1 26:2,13,21 31:14,16 36:1,4 42:4,8,21 43:1,2,7,10,16</p>	<p>44:8,12,17 45:4 48:11 49:8,11 50:17 63:22 64:2,5,15 65:9,13,18 66:1 67:5,10,12,15 83:19,21 84:2 89:11 90:3,18,20 91:2,14 92:1,5,12,16 106:22 107:2,13 108:7,8,11,14 109:7,8 112:19 123:11,16,22 124:10 125:2,6 126:10,19,21 127:4,22 129:3,5,15,22 130:13 131:18 132:7 133:8 134:5 136:22 137:2 138:7,18 139:18 140:9,10 141:22 142:19 144:2 146:5,6,13 147:2 149:2,8 150:9 152:2 153:15 154:6,8,9 155:16 157:14,15,17 158:5,8,13 160:11 161:13 162:9 165:6,20 166:7 167:7 169:21 171:4,6,12 175:21 176:9,18 177:8 178:16 179:22 180:3,19 181:1 182:1 183:1,11 184:10 185:2 186:1,18 187:5,19 188:4,10 189:11,13,15</p>
---	--	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 14

<p>190:8 drag 148:22 dramatic 85:19 133:7 draw 41:9 drive 106:3 driven 163:17 dropped 86:3 DrPH 2:12 5:3 drug 1:2 4:5 5:8 6:5 11:17 30:10 34:3 42:20 49:10 55:3 62:6 84:1 85:3,5,9,10 90:9,13 93:2 94:4,11,19 95:3 96:3 97:8,12,14,15,20 100:21 103:8,19 106:16 108:22 109:2,10,15 111:1,3,5,6,7 113:3 115:14 120:16 123:18 127:13 139:8 140:18 141:15,20 142:12 149:10,12 155:10 159:11 161:16 164:1,21,22 167:17 169:16 173:2 175:1,10 176:17 178:6,13 184:8,19 185:8 186:7 187:7 188:15,16 drugs 1:5 4:5 6:6,11 9:10 10:19 11:21 23:1,4,16 27:18</p>	<p>28:6 33:21 36:7 42:14,16 49:16 55:15 62:13,20 70:16,22 81:16 85:14 90:6 93:1 96:11,14 98:7 99:9,15,16 103:21 120:5 138:20,22 139:6 147:12 151:1 155:13 156:8 158:16 185:3 187:15,17 ductus 75:6 due 30:3 39:9 142:12 duly 191:5 dunk 185:5 duplicate 101:3 duration 36:15 during 1:5 6:11 7:8 8:5,9 9:6,10,20 10:11 11:18 12:4 13:7 14:5 15:14 17:20 18:17 23:22 27:20 34:2 39:21 40:6 42:15,20 45:6 48:5,6 54:1 74:5 75:3,21 77:20 93:6,11 113:11 116:19 117:22 120:6 133:18 139:21 143:4 159:3 166:15 179:5 181:12 dynamics 73:10 E eager 14:16 18:13</p>	<p>137:10,11 earlier 81:20 114:5 116:11 119:8 121:18 132:3 176:13 184:10 early 25:10 54:11 58:2 61:21 69:14 85:12 86:14 87:3 106:18 113:11 129:18 150:2 easier 127:19 130:9 186:9 easily 55:21 East 132:12 easy 133:10 137:18 138:1 155:22 159:17 177:22 echo 163:5 164:8 ecological 46:8 ecologically 52:20 economical 101:6 edge 20:1 edition 24:10,12 educating 177:19 education 80:17 educational 122:1 effect 32:21 35:11 77:1 175:13 effective 17:19 93:15 106:13 147:6 165:17 effectively 134:19 164:16 effectiveness 33:3 105:21 150:22 effects 45:9 52:10</p>	<p>127:14 178:19 efficacy 28:2 146:16,18 efficiency 45:2 62:11 efficient 63:10 101:9 148:14 effort 6:17 15:2,3 28:14 101:22 154:20 184:13 efforts 13:13,15 32:21 65:11 100:14 101:3 176:19,20 either 28:5 39:21 46:12 93:5 94:14 112:22 116:10 120:2 138:22 166:17 172:14 173:8 179:11 183:17 elaborate 126:17 elective 119:17 electronic 34:5 element 107:5 114:16 116:5 117:9 119:9 elements 112:5,12 elevated 61:6 99:18 eligible 94:3,7 101:20 eliminate 29:4 Elise 2:5 24:2 Elise's 84:15 else 175:9 177:6 EMA 110:6 embark 17:8</p>
--	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 15

<p>embryo 134:3</p> <p>embryonic 161:21</p> <p>emergently 89:21</p> <p>emphasize 17:21 83:12 135:16</p> <p>emphasizes 132:20</p> <p>employed 191:10,14</p> <p>employee 191:13</p> <p>encountered 178:22</p> <p>encourage 7:17 136:12 148:8 154:21</p> <p>encouraged 65:5</p> <p>encourages 106:11</p> <p>encouraging 37:15 83:1,14</p> <p>endeavored 178:18</p> <p>endless 147:22</p> <p>Engaging 106:17</p> <p>English 129:10,12</p> <p>enhanced 28:20 40:5 101:18</p> <p>Enjoy 190:6</p> <p>enormous 132:10</p> <p>enroll 48:18,19,21 49:19 50:10 52:8,9,13,22 53:5 54:15,20 55:17,19 58:7 59:11 62:20 64:7,12 65:6 68:19 69:15 76:2 80:7 81:20 83:8,9 87:7 136:17</p>	<p>137:10,19 139:7,13 140:19 150:12 154:16,17,21 170:6,8 176:22 181:8,10</p> <p>enrolled 48:4,22 50:13 53:3 54:1,3,8 55:20 56:15,16 57:11 58:18 60:10,17 61:10,12 69:19 78:14 79:9 81:19 85:18 90:7 98:2 132:22 139:16,17 170:4,10 180:13 181:4</p> <p>enrollee 133:1</p> <p>enrollees 69:15 79:1,8 86:5 89:2 134:10 135:9 137:15</p> <p>enrolling 35:19 51:10,17,19 52:2 53:11,17 68:18 80:16 144:16 152:5 155:6 159:3</p> <p>enrollment 16:1,20 30:3 33:9,10 36:12 39:2,3,5,9,14 42:12,19 50:1,20 51:10 55:6,12 56:13 57:7,9,18 58:3,6,14,15 64:6,13 86:20 89:9 105:8 113:11 114:4 126:5 129:21 136:13 137:7 139:12,20 148:3</p>	<p>154:15 182:13</p> <p>enrollments 34:21 98:6 176:6</p> <p>enrolls 49:15 135:18</p> <p>ensure 35:1 106:18</p> <p>entire 57:19</p> <p>entirely 17:2 167:21</p> <p>epidemics 166:13,14</p> <p>epidemiologic 46:14 128:19</p> <p>epidemiologist 21:4 22:9,14 26:1 44:16 84:9</p> <p>epidemiologists 31:9 64:20</p> <p>epidemiology 4:8 5:4,11 21:13 22:22 23:11,20 24:22 27:10 47:20 51:8</p> <p>epilepsy 50:5 84:10 147:21</p> <p>epileptologists 147:18</p> <p>equipment 76:5 112:15</p> <p>equivalent 187:16</p> <p>Erick 1:19 191:2,19</p> <p>especially 120:20 127:14 141:15 176:14</p> <p>essential 69:6</p> <p>essentially 77:10</p>	<p>158:2 174:21</p> <p>establish 111:22 112:4,7,14 119:10 125:12 146:18</p> <p>established 21:20 49:13 102:22</p> <p>establishing 111:18 180:5</p> <p>establishment 101:3</p> <p>estimates 173:18</p> <p>et 40:19 50:6,15 89:7 124:13 170:18 172:2</p> <p>ethics 45:17</p> <p>Eurocat 72:2</p> <p>Europe 111:15</p> <p>European 40:4 72:2 110:6 112:9</p> <p>evaluate 1:4 6:10 9:9 28:22 30:21 31:21 48:8</p> <p>evaluated 32:10 35:13 36:6 120:3 158:20</p> <p>evaluating 51:4 99:9</p> <p>evaluation 4:5 6:5 13:6 22:16 35:18 101:17 109:12 119:22 120:1 170:18</p> <p>evaluators 101:12</p> <p>event 58:2,18 108:17 118:15,22</p> <p>events 58:14 62:14 117:11 119:7</p>
--	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 16

<p>124:13 126:4 128:22 170:21</p> <p>everybody 17:13 27:1 73:16 126:1 142:1 160:9 169:6,8 174:19,21 175:5,9,19</p> <p>everybody's 148:22 188:14</p> <p>everyone 31:15 68:4 108:3</p> <p>evidence 24:7 119:4</p> <p>evolved 88:13</p> <p>evolves 134:2</p> <p>exact 65:1</p> <p>exactly 173:12</p> <p>exam 83:5</p> <p>examination 133:15</p> <p>examined 70:11,17</p> <p>examiner 70:20</p> <p>examines 73:1</p> <p>example 37:10,21 47:6 48:17 49:7 51:2 55:10,14 60:5,6,8 65:18 71:19 78:21 79:9 95:11 121:15 122:5 125:10,21 127:12 133:8,10 159:10 174:18 178:9</p> <p>examples 93:19 97:7</p> <p>exams 71:7</p>	<p>exception 99:16</p> <p>excess 95:9</p> <p>excited 26:7</p> <p>exclude 45:15 53:14 79:22 82:9</p> <p>excluded 27:17 74:7</p> <p>excluding 39:14 74:21</p> <p>exclusion 68:14 70:7,9 71:17 75:15 166:12 174:2</p> <p>exclusions 72:20 73:8</p> <p>excuse 144:4</p> <p>exist 97:6</p> <p>existence 171:22 176:15</p> <p>existing 30:17 185:20</p> <p>exists 29:7</p> <p>expand 13:2 125:3 184:8</p> <p>expanded 96:16 97:21</p> <p>expect 26:9 53:3,22 57:5 60:1 128:11 142:5,8 143:16 173:11 174:9 180:21</p> <p>expectation 123:18</p> <p>expected 12:4 48:9 60:19</p> <p>expense 147:15,17 184:13</p>	<p>expensive 159:2</p> <p>experience 9:16 12:7,13,19,20 13:10 60:9 92:18 103:21 109:6 122:1 125:7 129:18 155:18 166:2</p> <p>experiences 14:17 108:10 130:22 131:6 188:6</p> <p>expert 106:14 178:2</p> <p>expertise 30:14 40:19 102:15 168:14</p> <p>experts 30:15 101:11 104:21 166:1</p> <p>explain 19:17 113:12 122:6</p> <p>explained 46:10 112:5 114:5 116:11 121:18</p> <p>explaining 112:16</p> <p>exploratory 12:19 27:7 30:21 31:19 40:8 41:1,10</p> <p>explore 41:17 122:2</p> <p>explored 130:11</p> <p>exposed 42:16 47:3 48:14,15 49:15,18 51:13 53:21 54:1,5,6 56:9 57:20 58:13 59:11,20 60:2 63:2 76:13 77:16 81:10 89:16 98:13,14 99:14</p>	<p>116:9 137:13 139:4,8 140:22 141:4 155:10,13 158:16</p> <p>exposure 9:18 10:6,10 12:3 13:5,7 14:18 15:7 16:7,13 22:3,15 26:11 28:17 29:17 30:2,22 31:2,20 32:8 34:1 41:14 43:21 44:6 48:20 62:6 74:5 78:21 81:11 89:8 93:9 94:4 95:18 98:12 109:2 110:7,14,21,22 111:4 113:22 114:8 116:19 120:3,16 130:17,21 131:7 138:13 139:3,13 141:13,18,19 142:3,6,14 144:6,17 147:13 161:19,21 163:2 179:14 189:7</p> <p>exposures 9:22 11:3 13:3 40:6 62:19 81:1 95:13 96:7,11 99:2,12 100:8 108:5 110:2 143:1 144:9 145:6 149:14 153:19 155:21 163:10 170:7 177:2 179:7,9 183:20</p> <p>expression 189:4</p> <p>extend 187:6</p> <p>extensive 33:17 34:21</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

<p>extent 150:4 external 63:8 extra 7:11 extracted 32:8,18 extreme 163:4 extremely 73:5 74:2,4,20 75:22 80:1 128:12 extremes 171:3</p> <hr/> <p style="text-align: center;">F</p> <hr/> <p>face 120:14,17 121:3,8,13 147:21 faced 128:2 facilitate 126:4 facilitating 105:10 facing 120:17 122:6,16 127:9 130:8 FACOG 3:11 4:13 fact 15:19 42:14,15 77:21 131:2 132:20 138:9 145:7 149:18 164:3 175:11 177:1 182:6 187:11 189:6 factors 30:7 40:17,20 189:3 fail 30:2 104:5 failing 104:4 failures 12:11 fall 155:12 169:5 false 46:6 familiar 85:22</p>	<p>166:5 family 49:17 55:17,19 69:19 81:19 90:21 175:9 fascinating 87:2 fast 183:22 184:7 faster 148:18 186:9 fatal 109:17,20 fathers 158:22 favor 162:11 FDA 1:2,15 3:3 4:12 6:16 7:14 8:19 10:15 11:13 12:5,17,20 16:10 18:20 19:7 20:18 22:18 26:19 28:8,20 29:19 31:17 32:4 33:18,20,21 34:3 35:9 48:11,19 68:1 72:12 81:6 83:13 108:15 112:6 113:2 117:8 123:20 124:20 141:16,18,19 166:10 167:6,15 169:15 FDA-2014-N-0157 1:9 FDAAA 11:12 35:10 FDA's 22:15 187:14 fear 134:17 176:7 feasibility 39:8 feasible 96:9 162:3</p>	<p>163:22 features 34:12 federal 13:13,15 28:9 118:18 feedback 7:19 feel 89:4 feeling 167:9 feet 187:14 fellow 4:15 27:9 31:12,16 female 141:14 females 12:2 30:9 142:3 175:6,11 fertility 52:10 fetal 95:8,13,18 119:17 132:18 133:16 fetus 45:9 53:7 134:3 153:1 fever 143:7 188:20 fewer 42:15,16 field 17:9,12,14 18:5 19:1 fields 35:2 104:22 fifth 74:12 Fifty-nine 36:5 Fifty-three 36:13 figure 86:8 104:17 142:16 179:14 final 29:5 33:19 37:12,14 38:10 164:7 188:9 finalized 29:2 finally 115:20 financial 105:13 financially 191:14</p>	<p>finding 64:13 74:7,15,22 78:7 84:22 86:20 128:16 148:19 findings 71:7 73:11 74:18 75:8,20,21 77:7,9 78:3 79:16 84:11 85:10,18 86:10 87:12 156:1 finds 100:6 fine 136:4 174:8 finger 74:12 fingers 19:14 first 8:6,16 9:4 10:14 26:13 33:4 38:3 43:17 44:8,18 52:21,22 54:2 60:17 61:11,15 69:21 85:5,18 89:3 90:4 92:22 93:22 95:2 98:12 99:2,14 100:8 102:13 103:3 108:17 125:9 130:16,18 151:7 154:13 155:20 161:18,19 170:2 173:9 five 70:3,16 180:17 fivefold 56:14 57:1 59:18 fix 131:4 fixed 170:14 flat 19:13 flip 145:10 flow 131:8 137:3</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 18

<p>flu 111:14</p> <p>Fluzone 121:20,21 125:22</p> <p>focus 12:12 13:19 14:6 16:6 27:22 35:7 44:22 47:22 50:16 51:8 59:2,7 63:10 67:21 69:11 131:5</p> <p>focused 130:15 161:16</p> <p>focuses 23:22</p> <p>focusing 17:2 68:12 73:12 164:13</p> <p>folate 144:11,14</p> <p>folks 14:11 68:8 80:18 83:11 84:7 87:16 131:16 141:11 148:6,12</p> <p>follow-up 39:11,15,17 63:15 98:6 112:17 117:10 121:4,8 122:13 128:9 129:20 159:22 180:1,17,20 182:9,15,20,22</p> <p>follow-ups 155:1</p> <p>FOOD 1:2</p> <p>foramen 75:7</p> <p>foregoing 191:3,5</p> <p>form 83:1 113:3 118:5 154:15</p> <p>format 29:3 37:16 38:2</p> <p>former 22:15</p>	<p>forms 134:11 136:8 181:17</p> <p>formulary 143:20</p> <p>formulations 94:20</p> <p>forth 76:7 77:7 83:5 84:19 87:17 163:14</p> <p>fortunate 84:3 147:9 160:3</p> <p>Fortunately 74:22 179:5</p> <p>forward 17:5,9 41:7 83:16 132:1 138:16 187:4</p> <p>fourth 117:9</p> <p>fragile 160:2</p> <p>framework 94:16</p> <p>frequency 34:14 48:9 70:2 73:7,9 78:17,20 79:5,19 85:19 100:7</p> <p>frequent 97:3</p> <p>frequently 103:3 117:15 171:17</p> <p>friend 55:19</p> <p>friends 49:17 55:16 69:19 80:11,12 81:19 90:21</p> <p>front 148:15 178:10</p> <p>frontline 164:19</p> <p>fruition 6:18</p> <p>fulfill 93:11 118:21</p> <p>full 144:8</p>	<p>function 162:4</p> <p>funded 39:22 78:1,6 100:12</p> <p>funding 64:8 79:7 87:6 106:3 160:1</p> <p>funds 168:2</p> <p>fuzzy 144:1</p> <hr/> <p style="text-align: center;">G</p> <hr/> <p>gain 106:17</p> <p>games 62:2</p> <p>Gardasil 38:17</p> <p>gather 14:10</p> <p>gathered 9:6</p> <p>general 24:16 49:14 63:5 72:14 76:3 79:16 86:7 113:14 117:16 172:21</p> <p>generalizable 90:22</p> <p>generally 10:21 93:5 171:17 186:16</p> <p>generate 162:6</p> <p>generated 18:21</p> <p>generating 123:4 157:4</p> <p>generic 95:14 171:20 186:14 187:13,20</p> <p>generics 186:20 187:15</p> <p>genes 189:3,4</p> <p>genetic 72:10</p> <p>genetics 73:16 189:1</p>	<p>Geneva 108:20</p> <p>geographical 46:9</p> <p>Georgia 21:6</p> <p>germane 179:17</p> <p>gestation 48:5 50:2 75:5</p> <p>gestational 55:6 58:3 118:10 179:14</p> <p>gets 71:10 168:21 170:20 180:9 183:22 184:7</p> <p>getting 152:18 156:6 168:8 175:7 177:11</p> <p>gist 70:9</p> <p>given 13:14 44:1 65:18 96:21 146:2 155:10 160:9 179:16 191:9</p> <p>gives 106:9</p> <p>giving 109:21 140:3 150:1 179:18</p> <p>glad 65:13</p> <p>GlaxoSmithKline 157:6</p> <p>global 5:14 111:12,13 117:14 118:20,22 121:21 125:4 126:12,18,20,22 127:8 128:2</p> <p>globally 122:2 127:6,20</p> <p>goal 41:18 93:11 150:11 157:12</p>
--	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 19

<p>160:6 162:13 goals 4:6 8:17 149:14 150:14 156:20 163:16 God 144:10 gold 142:11 169:7 gone 85:11 152:14 goodwill 87:8 Google 82:17 Googling 74:15 gotten 12:15 42:19 168:3 governance 83:22 100:17 104:12,17 105:12 107:4 government 104:22 108:18 162:15 grading 168:20 gradually 88:17 grail 128:17 graph 55:5 61:7 graphs 54:4 grateful 87:12 great 1:16 25:18 26:2 67:4,8 73:4 79:19 107:3 126:13 150:1 161:14 168:9 176:20 greater 36:17 73:8 140:13 greatest 106:18 Greek 56:18 Greene 2:10 24:15 42:8 43:1,7</p>	<p>65:18 123:16 129:5 131:21 133:8 139:18 141:22 142:19 153:15 154:8 178:16 183:11 188:10 group 5:6 11:7 24:5 48:10 49:17 51:14 53:22 54:3,7,15 63:7,8 67:14,22 68:15,16 69:11,12,18 72:18 76:12 77:16,19 78:15 79:10 80:8,14 82:21 83:15 85:20 86:13 90:22 91:5,10 98:21 115:19 121:14 128:17 129:1 146:15 148:5 150:8,18 151:3 161:4,12 166:19 171:11 183:19 184:20 188:2 groups 45:6 50:9,18 53:21 55:16 57:21 58:13 67:11 90:16 91:9 104:1,20 110:15 147:18 159:20 167:13 171:9 GSK 115:9 guess 43:16 85:6 126:15 160:13 guidance 10:15,16 28:17 29:11,15 30:7 35:9 65:20 106:8 111:19</p>	<p>112:2,5,10 167:10 168:4 176:13 guidances 111:21,22 guide 24:11 guidelines 33:12 38:14 41:3 48:12 112:12 113:2 114:16,18 119:9 168:4,12 guys 167:2 <p style="text-align: center;">H</p><hr/>half 9:7 14:7 26:8 98:5,11 158:19 160:5 163:9 half-year-old 159:21 Hammad 3:4 4:14 12:18 27:9 31:11,14,15 Hampshire 1:15 hand 66:5 114:11 117:1 handbook 24:11 handful 46:1 hands-on 166:2 Hansen 2:11 21:3,4 happen 53:1 91:11 153:2 166:20 185:7 happened 114:14 167:22 happens 10:7 57:5 65:6 117:21 156:13 185:10</p>	<p>happy 42:1 137:12 hard 66:20 144:13 160:2 harder 129:14 hardworking 75:11 harm 177:12,22 Harvard 5:4,8 23:21 haven't 79:17 81:21 90:11 having 20:12,19 25:10 50:13,22 53:10 63:3 84:3 85:13 87:13 110:1 118:19 123:6 127:20 132:5 142:11 151:3,16 152:14 157:20 184:14 186:11,19 head 90:19 headache 143:8 heads 68:8 health 4:4 5:5 6:7 14:13 19:7 21:5 22:13,17 23:5,8,15,21 25:13,15 26:16 28:8,10 30:12 32:17 40:11 41:19 52:17 86:19 93:12 101:5,21 102:5 110:17 114:14 115:2 116:2,7,8,17 117:7,19 120:21 121:3,4 125:15,17 145:11,17</p>
--	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

<p>163:18 175:16 182:5,6,12 186:3,16</p> <p>Healthcare 24:3</p> <p>hear 14:16 18:13,18 25:8,20 47:15 91:6 131:2 146:22</p> <p>heard 97:10 152:3,4 176:18</p> <p>hearing 41:8 188:6 191:3</p> <p>heart 89:6</p> <p>heck 179:20</p> <p>hello 20:7 21:12 25:8 89:11</p> <p>help 24:8 26:10,22 30:18 69:2 83:4 122:22 146:20 152:7 153:6,7 168:13 181:15,22</p> <p>helped 129:19 168:14</p> <p>helpful 18:11 106:7 110:8 148:19 168:6 169:19 173:21 174:7 175:22 185:1 188:6</p> <p>helps 181:11</p> <p>hepatitis 97:16,17 183:18</p> <p>HER2+ 96:16</p> <p>herbals 144:9</p> <p>herd 175:13</p> <p>hereby 191:3 192:2</p>	<p>hereditary 74:7</p> <p>Here's 28:12</p> <p>hereto 191:14</p> <p>Hernandez 23:19 44:8 186:1</p> <p>Hernandez-Diaz 2:12 5:3 23:19 44:12 64:15 66:1 150:9 169:21 181:1 186:1</p> <p>herself 26:14</p> <p>Hi 21:22 22:11 44:12</p> <p>high 12:1 76:20 89:9 93:7 95:5 97:2 102:15</p> <p>higher 48:9 86:6 144:17 159:11,13</p> <p>highlight 121:18</p> <p>high-risk 140:18</p> <p>hinges 106:13</p> <p>HIPAA-compliant 113:19</p> <p>historical 69:10 77:18 79:13 91:9</p> <p>historically 177:10</p> <p>history 10:14 27:3 28:13 33:22 120:4</p> <p>hit 20:3</p> <p>HIV 97:15,16</p> <p>HMO 22:2 47:11</p> <p>Hoda 3:4 4:14 12:18 27:8 31:11,15 36:4 42:3</p> <p>hold 107:17 108:4</p>	<p>175:18</p> <p>Holmes 2:13 5:7 21:9,10 44:17 49:8,11 50:17 64:15 65:9 67:10,12,15 83:21 84:2 90:3,20 91:2 112:19 132:7 134:5 146:13 147:2,3 158:13 166:7 184:10,11</p> <p>holy 128:17</p> <p>home 75:4</p> <p>homeboxes 189:3</p> <p>hone 146:3</p> <p>Honein 2:14 25:19,21,22 157:15,17 158:8</p> <p>hope 26:9 43:19 81:21 127:8 131:8</p> <p>hoping 26:4</p> <p>horseshoe 20:2</p> <p>hospital 24:17 49:14 71:4 75:3 77:3 172:15</p> <p>hospital-based 172:12</p> <p>hospitals 70:16 172:9</p> <p>hot 150:22</p> <p>hour 8:5 189:22</p> <p>housekeeping 6:20 91:16</p> <p>huge 46:19 59:10 60:20,21 61:16 66:8 147:17 148:2 170:5</p>	<p>179:6</p> <p>human 9:12,16 27:19 38:17 93:9 149:21 164:22</p> <p>humans 45:14</p> <p>humatirogene 78:21</p> <p>Humira 38:14</p> <p>hundred 155:20</p> <p>hundreds 32:13</p> <p>hydronephrosis 76:22 77:10 133:9,12,17,22 166:14</p> <p>hypotheses 162:6</p> <p>hypothesis 123:3</p> <hr/> <p style="text-align: center;">I</p> <hr/> <p>ICD-9 75:10</p> <p>I'd 67:5 92:12 108:7 157:14</p> <p>idea 59:7 72:16 82:17 85:8 88:14 91:8 122:14 154:15,21 155:6 170:22 173:22</p> <p>ideal 46:12</p> <p>ideally 52:22 54:8 113:8 154:17</p> <p>ideas 15:15 18:18,21</p> <p>identified 29:22 39:21 77:5 94:3,8 162:20</p> <p>identify 15:7,8 34:5 123:1 145:6 155:2 163:4 164:1,16 172:6</p>
--	--	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 21

<p>identifying 106:13 141:3 165:5</p> <p>ignore 138:1</p> <p>I'll 27:13 31:17 64:17 70:8 136:19 142:19 143:18 145:20 162:11 164:8,10 167:20</p> <p>I'm 22:6 24:15,19,21 26:1 58:19 97:18 100:19 112:4 115:21 130:2 144:21 150:10 155:4,13 158:9 160:8 177:1 183:10</p> <p>imagine 87:15 144:13 145:3 160:3 175:1</p> <p>imaging 75:1,2 79:19</p> <p>immediate 139:22</p> <p>imminent 177:22</p> <p>Immunization 124:8</p> <p>impact 42:10 132:5</p> <p>imperative 93:13 104:10</p> <p>implantation 132:4</p> <p>implement 102:16</p> <p>implementation 15:17 30:8,19 93:22 103:4 106:12 129:16</p> <p>implemented</p>	<p>12:10 35:15 93:5</p> <p>implementing 14:17</p> <p>implications 51:7 52:4 145:11</p> <p>implies 94:18</p> <p>importance 28:1 72:7 83:13 89:5 109:9 110:2 145:18 157:20</p> <p>important 8:21 13:22 15:11 20:13 28:5,7 51:3 71:19 82:14 86:14 89:15 92:21 102:1 107:5 108:16 111:22 112:12 114:21 123:8 135:16 139:9 149:17 150:7 156:19 157:11 176:11</p> <p>improve 15:8 17:17 18:5 29:5 41:6,19 129:20 130:1</p> <p>improved 12:16</p> <p>improvement 31:6 41:5</p> <p>improves 186:6</p> <p>improving 153:18</p> <p>inadvertent 12:3 40:6 139:2</p> <p>inadvertently 45:21 137:13</p> <p>INC 5:12 21:14 92:13 107:14</p> <p>incentive 102:6</p>	<p>incidence 56:19 58:11</p> <p>include 27:2 30:8 40:2,9 45:21 53:8 58:17 76:12,21 80:2 82:3,9 94:10 96:16 115:17 116:20 118:6,7,9,16 119:4,6 122:3</p> <p>included 15:21 29:8 31:8 33:6,18 34:17 35:7,14,20 36:12,21 40:12 154:14 172:19</p> <p>includes 28:18 32:7 35:21 96:14 110:12 144:9</p> <p>including 13:15 14:12 21:1,15 34:13,15 45:1 74:21 77:9 113:20 115:14 153:17</p> <p>inclusion 68:13 71:17 166:12 174:2</p> <p>increase 57:8 62:11 85:19 90:10 100:7 102:6 126:5 160:18 161:10,11 176:6</p> <p>increased 56:14,18 59:10,14,18 61:7,16 66:16,22 150:3,4</p> <p>increases 170:5</p> <p>increasing 127:7</p>	<p>143:1</p> <p>increasingly 138:1 143:19 150:7 183:16</p> <p>incredibly 159:2 178:11 180:9</p> <p>in-depth 103:22</p> <p>indicate 156:14</p> <p>indicated 10:2 11:20 96:14 97:15,16,17 138:21 139:6 176:8</p> <p>indication 35:12 50:5 63:4 93:6 95:4 96:1 151:2,8,10 188:19</p> <p>indications 150:19</p> <p>individual 99:15 100:1 103:18 156:7</p> <p>individually 97:12 99:11</p> <p>individuals 6:15 69:3,8 94:9</p> <p>industry 2:18 5:16 14:13 28:9 40:1 105:4 108:8,16,19 109:3,10 110:4,9 111:2,5,21 113:6 120:15 176:1,13</p> <p>industry-based 176:14</p> <p>industry's 28:15</p> <p>infant 25:14 54:10 75:5</p> <p>infants 70:15</p>
--	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 22

<p>74:3,4 75:1 134:12</p> <p>infertility 52:7</p> <p>influence 58:15</p> <p>influenza 109:22 138:22 140:5</p> <p>inform 14:5 15:11 17:18 18:4 27:19 28:6 41:16</p> <p>information 15:13 27:2,3 29:6 30:3 33:7 35:19 36:12 38:3,16 39:11 43:19 45:18,22 46:1 48:7 49:22 50:7 52:1 53:11 60:15 62:8 63:15 64:19 66:7,9,11 67:3 70:7 74:17 92:10 93:1 107:12 109:1,13 110:1 112:3 113:21 117:20 118:3,4,6,7,11 119:20 120:19 123:8 124:3 125:12 134:17 143:17 144:8,14 145:9 156:5,14 158:22 160:19 173:8 179:4,8 182:15 186:10</p> <p>informational 115:19</p> <p>informative 50:13</p> <p>informed 37:11,22</p> <p>informing 32:22 41:13 93:12</p> <p>infrastructure 30:17</p> <p>inhibitors</p>	<p>183:16,21 184:5</p> <p>initial 86:8 184:12</p> <p>initially 84:6,22 88:13 98:13</p> <p>initiate 93:13</p> <p>initiation 35:8</p> <p>initiatives 13:2 175:17</p> <p>input 14:10 15:15 17:6 29:12 176:1</p> <p>insert 33:6</p> <p>inserts 114:22</p> <p>inside 6:15</p> <p>insisted 77:8</p> <p>instance 128:6</p> <p>instead 82:15 125:14 147:16 183:17</p> <p>Institute 22:2</p> <p>instructions 8:8</p> <p>instructor 45:4</p> <p>insufficient 47:1</p> <p>intake 62:18</p> <p>intentional 9:18 141:14</p> <p>interaction 105:11</p> <p>interactions 105:10</p> <p>intercurrent 163:10</p> <p>interest 18:15 24:6 47:4 48:3 52:19 54:6 58:21 144:6 156:4 181:5</p> <p>interested 34:13 52:16 63:13 87:9 91:12 124:19</p>	<p>161:22 190:4 191:15 192:6</p> <p>interesting 45:16 86:21 91:6</p> <p>interfaces 133:11</p> <p>interim 38:9 149:16</p> <p>intermediary 180:8</p> <p>intermediate 165:2</p> <p>internal 33:18 69:12 72:17 76:11 91:5 97:4 150:8,17 151:3 166:19 173:17</p> <p>internally 99:5</p> <p>international 37:19 111:10 129:7</p> <p>internet 84:17</p> <p>interpret 105:3 160:21</p> <p>interpretation 161:8</p> <p>interquartile 39:19</p> <p>Intervader 103:2</p> <p>interval 66:8 98:19 99:4</p> <p>intervals 57:13 61:17,19</p> <p>interventional 112:21</p> <p>interview 62:17 68:21 69:1,5 159:5 163:13</p> <p>interviewing</p>	<p>132:22</p> <p>interviews 50:1,3 82:22</p> <p>introduce 8:8,15 19:3,19,20 25:20 26:13 108:7</p> <p>introduced 26:14</p> <p>introducing 26:7</p> <p>introduction 4:2,19 6:2 9:4 43:15 44:19 45:3</p> <p>inundated 175:15</p> <p>investigating 187:10</p> <p>investigation 123:5</p> <p>investigational 27:17</p> <p>investigations 123:2</p> <p>investigator 22:1 25:15 49:9</p> <p>invitation 69:5</p> <p>invite 55:18 67:10</p> <p>invited 87:22 91:17,21</p> <p>inviting 44:13 64:7 67:13 108:15 153:5</p> <p>involved 20:9 22:3 107:10 162:18</p> <p>involving 30:15</p> <p>IQs 158:22</p> <p>IRB 105:10 154:19</p> <p>isn't 142:21 161:17 176:16 177:17</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 23

<p>issue 11:17 28:8,22 29:22 65:16 66:12 67:21 68:20 69:21,22 74:20 75:17,18 76:18 78:4 79:18 85:16 86:16 133:20 134:6,8 135:19 140:12,16 144:20 145:17 152:9 157:18 159:8 160:12 176:22 187:8,14,18</p> <p>issued 29:20</p> <p>issues 13:3 18:10 50:19 77:21 107:7,12 134:9 136:6 139:19 144:22 146:2 159:14 161:2 163:5 167:11 172:3 180:1</p> <p>issuing 11:11</p> <p>items 68:13</p> <p>it's 13:11 15:20 25:10 43:7 48:13 51:9 57:13 60:4,20 61:6 62:1 66:20,22 68:9 76:3 86:4,9,22 87:1 89:11 107:3 111:6 112:21,22 113:17,19 114:2 121:21,22 124:15 129:14,22 130:7 132:12 133:19 135:13 136:10,21 137:22 140:13</p>	<p>141:13,15 144:2 145:2 147:3,12 148:14 156:6 159:7 160:2,5,15 161:9,14 163:11 167:14,21 168:15,20 171:1,4,21,22 172:1,16 174:8 176:7 177:8,22 178:5,15 181:7 184:18 185:5 188:19</p> <p>Iyasu 3:6 4:7 8:16,18 19:9 22:20,21 48:11 107:2 109:7 160:11</p> <p style="text-align: center;">J</p> <hr/> <p>Jan 20:20 84:7 155:16 162:5 167:7 171:6</p> <p>JANET 2:9</p> <p>January 32:9</p> <p>Jessica 2:3 5:10 21:12 175:21 186:18 187:6</p> <p>Jessica's 176:10</p> <p>job 141:21 168:9</p> <p>Johnson 2:15 24:19</p> <p>join 26:3,5 188:1</p> <p>joining 131:16</p> <p>journal 34:19 38:8,11</p> <p>journals 33:14 115:18</p> <p>judgment 75:15</p>	<p>July 98:1,9</p> <p>jumps 133:12</p> <p>June 7:18 122:7</p> <p style="text-align: center;">K</p> <p>Kaiser 21:5 47:13</p> <p>key 34:12 35:2 68:20</p> <p>kidneys 133:16</p> <p>kids 163:9,12</p> <p>kinds 67:2 113:9 119:4 126:6 130:19 156:11,22 157:2 165:15 175:16</p> <p>kiosk 7:22 91:19</p> <p>kiosks 8:3</p> <p>knew 85:2 147:10</p> <p>knowledge 11:14 152:8</p> <p>known 11:5 48:5,21 74:5 95:8,12 114:13 149:21 152:20 162:16</p> <p>knowns 162:16</p> <p>Kweder 8:22 19:12</p> <p style="text-align: center;">L</p> <hr/> <p>label 15:21</p> <p>labeling 15:11 28:21 29:1,4,9 33:5,21 34:1,16,17 35:20 36:13,20 37:10,13,15,22 38:7 39:22 40:21 41:3,16 114:22</p>	<p>labels 64:18</p> <p>labor-intensive 158:21</p> <p>lack 63:7 67:3 121:9</p> <p>lactation 28:4 29:1,3 37:13</p> <p>lamotrigine 55:13 60:9,11,13,15,16 ,17 61:11 80:14 85:16 155:21 157:7</p> <p>landlines 137:17</p> <p>landscape 106:16 141:4</p> <p>language 129:9</p> <p>large 45:20 95:20 142:3,13 157:13 170:9</p> <p>largely 128:18</p> <p>larger 61:5 67:6 127:5 132:16 170:15</p> <p>last 16:3 17:5 18:7 20:10 68:13 83:3 118:10 119:9 136:11 158:7 165:12 168:10</p> <p>lastly 26:2</p> <p>late 9:1 53:3 63:13 133:14 171:22</p> <p>lately 127:9</p> <p>later 11:2 16:19 48:21 51:20 54:3,15 55:18 70:8 99:5 100:18 101:14 115:22 121:13 133:17,18 159:7</p>
--	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 24

<p>164:5 181:21 latter 94:5 lay 9:5 lead 22:15 26:10 learn 9:21 31:6 learned 45:4 61:20 62:1 85:5 189:1 learning 160:8 least 15:11 49:2 53:18 66:18 90:7 128:2 139:13 158:19 169:3,17 170:7 174:16 175:7 187:21 leave 64:17 lectures 115:20 led 25:14 legal 177:13 legislation 11:13 less 36:15 39:14 94:5 137:17 145:5,18 178:5 180:17 lesson 61:20 62:1 let's 10:1 70:10 73:10 78:8 letter 29:4 147:16 level 56:17,18 103:15,19 leverage 14:4 leveraging 13:17 30:17 Lew 44:17 49:8 131:21 149:8 163:6 173:5 Lewis 2:13 5:7 21:9 67:10 147:3</p>	<p>158:13 166:7 184:11 Lew's 133:8 Leyla 3:11 4:13 12:17 23:13 26:14,17 42:3 44:1 life 77:21 173:9 188:22 189:7 lifecycle 103:8 lights 43:10 likelihood 12:2 93:7 95:5 97:2 likely 48:14,15 96:4 132:13 179:2,19 Likewise 80:22 limitation 120:17 123:6 limitations 40:7 62:22 100:10 120:14 122:4,6 limited 63:18 87:6 101:10 111:4 122:15 limiting 128:12 line 138:17 167:8 170:2 171:1 175:19 lines 51:11 55:9 61:9 102:22 link 13:6 linking 13:8 lip 78:20 list 32:3 68:11 74:13 listed 40:8,10 72:22 74:1 75:11</p>	<p>79:12,14 80:9 100:13 listening 92:10 lists 79:14 147:14 literature 40:1 41:4 85:22 117:6 124:5,9 173:18 179:10 litigious 177:13 little 10:13 30:5 43:7,20 44:1 49:12 51:19 55:17 60:15,22 64:3,5,9 66:22 73:2 86:12 100:18 125:3 126:17 130:20 152:4 153:16 158:6 167:14 181:19 182:8 187:7 live 53:19 98:17 119:18 LLC 5:12 lobby 6:22 7:21 8:3 local 127:20 172:8 locally 127:6,17 location 111:9 logical 101:2 logistic 56:12 logistical 32:12 logistically 96:8 151:19 186:7,12 long 77:22 78:5 79:7 87:13 136:9 162:14 167:9 168:2 187:16</p>	<p>longer 138:5 189:7 longitudinal 62:15 longstanding 172:1 long-term 97:7 170:21 lose 149:17 loss 39:11,15,17 121:4 129:20 130:2,6 180:1,16,20 182:9,20,22 losses 50:22 52:11 63:15 lost 98:6 122:12 lot 14:1 16:6 18:15 67:2 68:6,7 69:10 70:4 73:2 74:22 76:3 86:1 88:13 109:1 120:21 126:8 135:5 138:4 143:19 155:21 156:5 164:14 180:10 185:6 188:16 lots 73:2 171:18 loved 148:9 lovely 25:5 low 30:3 39:9,14 184:22 lower 56:10 151:10 lowest 181:3 lunch 8:2,5 65:15 91:19 189:17,19 190:7 Lynne 3:10 4:10 19:3,4</p>
---	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 25

<p style="text-align: center;"><u>M</u></p> <p>MA 3:5</p> <p>MACDP 71:21 98:21 99:19 171:19 172:5 173:4,12,19,21 174:10</p> <p>MACDP's 173:16 174:8</p> <p>mailing 147:14</p> <p>mailings 148:11</p> <p>main 7:20 11:9 14:6 56:5 58:20 62:4</p> <p>mainly 45:21 113:21</p> <p>maintain 22:17</p> <p>maintained 76:8</p> <p>major 52:17 57:5 58:4 71:18 79:18 128:13 129:2 135:5 149:19 162:4 170:5 178:15</p> <p>majority 187:11</p> <p>Malaysia 130:4</p> <p>malformation 59:19 70:1,6 71:3 166:18 188:15</p> <p>malformations 52:18 57:5,11 58:4 59:2 73:9 79:5,6,12 85:15 89:1 146:3,4 159:12 161:4 162:4 170:5 171:20 188:17 189:6</p>	<p>mammalian 188:12 189:10</p> <p>manage 22:18</p> <p>management 5:15 103:9 105:5</p> <p>manager 4:3 6:4 23:7 24:20 69:13</p> <p>managing 105:7</p> <p>mandate 104:16</p> <p>manifest 162:22</p> <p>manufactured 96:22</p> <p>manufacturer 182:4 187:7</p> <p>manufacturer-run 182:3</p> <p>manufacturers 98:8 107:19</p> <p>manufacturer's 81:7 182:10</p> <p>manuscript 88:6</p> <p>MARGARET 2:14</p> <p>Marie 2:7 25:6,11</p> <p>Marie-Noel 77:2,4</p> <p>mark 42:17 141:6,7</p> <p>marker 141:17</p> <p>market 9:14 27:4 164:21 167:17 169:16 185:16 186:8 187:12</p> <p>marketed 95:4,15 96:20 164:2</p> <p>marketing 16:4 29:20 30:11 65:11 84:15 103:8 105:18</p>	<p>146:20 147:6,7 148:15 169:14 174:15 185:17</p> <p>Maryland 1:17</p> <p>masked 70:21</p> <p>mass 185:15</p> <p>Massachusetts 24:16 49:14</p> <p>materials 136:15</p> <p>maternal 4:4 6:6 19:7 23:5,8,15 26:16 120:4</p> <p>maternal/fetal 24:17 147:15 172:10</p> <p>maternal/infant 115:18</p> <p>math 186:6</p> <p>mathematical 59:22</p> <p>matter 76:3 129:5 163:11 184:9</p> <p>maximized 139:10</p> <p>may 1:12 7:7 12:4 15:21 30:7,18 40:17 41:15 42:17 48:16 51:13 53:9,18 54:19 57:14,20 58:3,4,15 62:22 63:2,4,8,9,14 64:16 66:4,8,9 73:3 94:9,10,20 96:6 97:6 103:11,12,15 106:4 110:13 118:15 123:5 128:22 139:10 144:17 145:8 149:2 151:11</p>	<p>160:19 161:8 164:4,5,22 165:7 170:7 173:1,3 179:16 181:15,17 182:6 186:14</p> <p>maybe 9:2 15:20 65:9 125:4 128:1,2 129:18 131:20 133:18 140:17 141:1 142:15 146:11 149:11 152:10 157:3 174:13 176:13 181:21 185:14 188:18</p> <p>MBDPS 47:21</p> <p>McNair 1:19 191:2,19</p> <p>MD 2:9,10,12,13,16, 20 3:6,9,10,11 4:7,10,13 5:3,7,14</p> <p>mean 14:22 40:22 86:17 89:1 114:2 115:14 122:21 126:10 129:12 140:1 144:12 145:4 147:21 155:6 156:2,12 161:9 162:21 163:22 175:17 178:14</p> <p>meaning 51:9 74:10</p> <p>meaningful 31:4 135:18 174:15 175:3</p> <p>means 13:8 80:22 113:10 115:17 116:3,20 157:5</p>
--	---	--	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 26

<p>176:21 meant 168:19 measure 161:4 measurement 80:3 160:19 measures 33:16 169:22 mechanism 102:7 mechanisms 162:5 median 39:17 Medicaid 47:11 medical 4:13 5:8 9:13 10:5,11 16:4 21:7 23:14 26:15 31:1,9 32:1,10,13,14 33:7 35:12,14,15 41:4 47:12 49:21 72:6 77:4 94:5 110:6 112:9 117:6 120:4 121:1 152:20 171:14 172:8 Medicare 24:5 medication 13:5 21:2,18 22:3,15 23:22 46:22 48:3 54:6,19 63:11 71:1 80:10 142:22 143:2 151:12 152:21 186:10 medications 14:19 15:14 17:20 47:3 51:13 55:8 57:22 62:11 63:3 69:4 85:1 139:20 143:4,20 144:5 169:14 170:7 179:2,16,18</p>	<p>medicine 24:17 25:12 137:11 147:15 172:10 meet 42:18 84:11 87:19 104:14 119:5 meeting 1:8 4:6 6:9,18 7:6,15,16,17 8:9,14,17 15:5 17:22 18:10 27:22 29:13 30:20 84:6,12 110:5 115:21 126:14 141:6 190:10 meetings 64:22 88:15 115:20 Melissa 3:7 4:20 23:3 134:5 178:16 member 55:19 84:8 members 8:7 31:8 49:17 55:17 69:19 81:20 101:12 147:16 Menactra 121:20 menstrual 118:11 mention 27:13 101:18 152:10 153:20 164:10 mentioned 48:11 49:5,7 69:18 82:15 125:6 137:19 142:1 151:20 184:10 mentor 104:4 MEPREP 47:15 Merck 20:8,9</p>	<p>115:10 128:1 message 82:3 102:9 140:6 177:22 messages 79:2 messy 142:15 met 42:11 88:15 107:21 method 125:15 153:20 methodological 44:22 50:17 94:13 167:11 methodologically 101:15 methodologies 14:4,8 15:4 106:6 methodology 5:2 27:11 31:13 40:16 44:10,11 151:4 methods 1:4 6:10 9:9 13:21 17:11 18:4 24:9 31:18 34:9 41:11,17 44:5 49:11 65:12 106:10 126:7 157:8 162:7 170:20 172:5 metric 175:5,7 metrics 174:16,22 Metropolitan 71:20 171:7,14 Mexico 125:10 Meyers 22:1 Michael 2:10 3:9 23:9 42:4 129:4 131:21</p>	<p>162:12,13 177:15 183:10 Michael's 144:4 microphones 8:10 middle 80:9,13 171:4 migraine 147:21 migraines 96:15 mike 18:16 20:3 24:15 123:12 132:10 139:18 140:16 142:19 153:15 178:16 183:11 185:7 188:9 Mike's 78:4 176:12 milestones 33:1 military 95:19 137:5 mind 53:2 54:14 76:19 140:1 156:20 157:12 178:12 188:14 mine 67:18 104:4 minimal 145:12 minimize 58:6 102:4 minimum 162:22 minor 73:8 77:6 minute 8:1 157:15 minutes 131:5 165:12 183:2 miscarriage 52:15 56:20 miscarriages 51:6 52:12 56:10 missing 51:5</p>
---	--	--	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 27

<p>120:21 121:1 135:5 158:1 misunderstanding 152:7 Mitchell 2:16 24:21 45:5 144:2 146:6 154:6,9 162:9 165:20 177:8 180:3 187:5 Mitchell's 142:20 mitigation 35:18 mixed 140:6 MMR 109:19 mobile 130:6 model 68:1 87:15 159:17 models 69:9 moderator 4:19 5:19 8:11 43:15 188:3 modest 81:11 99:17 modifier 144:7,18 modify 146:10 mom 181:16 moment 85:13 157:10 moments 64:2 moms 62:17 158:11 Monday 84:12 money 63:12 148:15,17 159:15 163:8 monitor 21:18 95:17 96:19 114:1 124:9</p>	<p>175:12 monitored 98:7 103:22 monitoring 113:4 141:3 167:16 monitors 94:19 95:13,22 96:10 97:11,13 monotherapy 90:6 97:12 103:19 montelukast 37:3 month 51:18 69:15,16 88:6 108:20 months 20:17,18 50:2 181:13,21 mood 54:20 morning 5:19 8:1,18 17:2 20:7,14 21:3,9 23:2,6,9,13 25:6,8 26:4,13 27:1 31:15 43:18 44:12 47:5 92:7,11,16,22 130:16 188:3,5 mostly 36:6 113:6 171:19 172:12 mother 73:3,14 77:8 96:15 139:1 172:17 mother-child 21:20 mothers 158:22 MotherToBaby 22:9 motivated 138:6 motivation 136:5 move 17:5 43:17</p>	<p>58:19 104:2 126:18,19,22 130:14 138:16 159:18 168:12 170:22 183:2 moves 132:2 187:4 moving 17:9 108:18 111:12 125:4,7 127:5 132:2,18 134:1 138:11 Moyer 3:8 4:3 6:3 23:6,7 MOYERS 42:2 43:9 91:16 131:13 189:16 MPH 2:3,6,7,9,14 3:4,6 4:7,14 5:10 multi 92:18 94:14 97:22 100:20 multi-drug 97:1 150:19 151:17 186:4 multinational 128:3 multiple 35:15 62:19,20,21 94:20 95:22 96:11 101:7 104:13 107:9 111:5 127:20 143:13 160:20 161:1,2 184:14 multi-product 5:9 92:14,15 93:17 94:16 95:21 96:18 97:22 100:22 101:8,14,19 102:2,13 103:17 183:8</p>	<p>multi-tiered 103:18 muscular 79:22 166:14 Mycophenolate 37:7 myself 66:3 152:15 <hr/><p style="text-align: center;">N</p><hr/>Naleway 26:3 Naratriptan 96:13 narrower 61:19 nation 177:13 national 20:21 37:8 40:4 178:18 native 129:9 nature 11:17 131:19 Naval 25:13 nearly 86:7,16 97:22 necessarily 32:6 88:10 146:9 174:10 necessary 103:6 151:14 negative 89:14 176:17 neither 35:17 191:10 192:5 nelfinavir 99:17 neonatologists 82:13 network 22:2 186:8 networks 47:11 neurologist 51:22</p>
---	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 28

<p>neurologists 64:19 82:1 84:8,18 147:19</p> <p>neurology 90:5 147:17</p> <p>newborn 173:8</p> <p>newborns 79:20</p> <p>newer 132:13</p> <p>newly 65:21 95:2</p> <p>news 86:11 90:8</p> <p>newsletters 115:19</p> <p>newspaper 123:21</p> <p>Nguyen 3:9 23:9,10 90:20 123:22 129:15</p> <p>nice 107:3 141:17</p> <p>nicely 142:21</p> <p>NIH 84:10</p> <p>nine 133:15,21</p> <p>Ninety 122:8</p> <p>none 61:4</p> <p>non-experimental 46:13</p> <p>non-exposed 150:17</p> <p>noninterventional 112:22</p> <p>nontraditional 125:9</p> <p>nonusers 56:10</p> <p>noon 8:3</p> <p>nor 191:10,14 192:5,6</p> <p>normal 75:8 81:8 133:16</p> <p>normally 145:14</p>	<p>North 5:7 21:10 49:9 55:3 60:7 83:22 97:8,10 132:8 147:3 155:18 158:14 166:8 181:6 184:11</p> <p>Northern 110:19</p> <p>notable 74:9</p> <p>nothing 66:9 184:5 189:14</p> <p>notice 73:3</p> <p>noticed 165:7</p> <p>notified 114:12</p> <p>notion 177:11</p> <p>nuances 106:16</p> <hr style="width: 20%; margin: 10px auto;"/> <p style="text-align: center;">O</p> <hr style="width: 20%; margin: 10px auto;"/> <p>Oak 1:15 25:5</p> <p>ob-gyn 23:16</p> <p>objectives 4:6 8:17 15:5 93:16 104:15 105:17,18,21 106:3,4</p> <p>obligation 36:10</p> <p>obligations 186:21</p> <p>observation 42:9</p> <p>observational 48:2 112:21 113:7 142:13,18</p> <p>observations 4:12 26:20 27:14</p> <p>obstetrical 132:11</p> <p>obstetrician 84:9,18 139:19</p> <p>obstetrician-gynecologist</p>	<p>24:16</p> <p>obstetricians 82:1</p> <p>Obstetrics 24:18</p> <p>obtain 48:7 134:11</p> <p>obtainable 162:3</p> <p>obtained 9:17 49:22 50:7 124:15</p> <p>obtains 49:19</p> <p>obvious 184:15</p> <p>obviously 80:3 81:13 148:9 182:16</p> <p>occasionally 88:1 124:2 133:4</p> <p>occur 103:11 145:12 171:17</p> <p>occurred 128:11</p> <p>occurrence 81:8 120:8,10</p> <p>occurring 132:14</p> <p>occurs 145:14</p> <p>o'clock 92:2 190:1</p> <p>offer 101:22 102:8</p> <p>office 4:5,7,8 6:6 22:13,17,21 23:4,15 27:9 32:4,17 40:10 124:8 159:18</p> <p>officer 4:13 23:14 26:15</p> <p>officers 31:9 117:15</p> <p>offices 31:10</p> <p>official 162:15</p> <p>offspring 52:17</p> <p>oh 19:3 26:22</p>	<p>143:9,14 156:4</p> <p>okay 9:11 19:4 26:22 71:14 78:8 91:15 129:4 143:21 146:7 154:8 158:9 189:15</p> <p>old 29:11 132:12,17 158:19</p> <p>older 72:4</p> <p>OND 4:5,10,13,21</p> <p>one-hour 189:17</p> <p>ones 59:4 67:19 123:22 127:20 135:9 181:10 187:20</p> <p>ongoing 39:7</p> <p>online 125:18,19</p> <p>OPE 4:8,15</p> <p>open 7:4,18 16:18 17:4 18:17,19 30:4 131:10 190:1</p> <p>Opening 4:9 19:10</p> <p>operating 166:4</p> <p>operational 105:14</p> <p>operationally 96:8 102:14</p> <p>operations 105:8</p> <p>opinion 185:2</p> <p>opinions 146:7</p> <p>opioids 174:18,19</p> <p>opportunities 13:16 14:1</p> <p>opportunity 92:17</p>
--	--	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 29

<p>139:5,10,11 opposed 74:11 88:14 options 95:10 105:18 oral 59:4 60:18 61:1 85:20 89:6 order 31:21 33:15 93:11 106:5 110:3 114:1 167:17 organ 160:20 161:2,5 Organization 38:15 organizations 28:11 ORISE 4:15 27:9 31:12,16 orthopedist 83:3 orthopedist's 83:5 OSE 4:8,15 31:12 OTCs 144:9 others 30:16 50:5 66:6 76:10 145:1 166:6,10 178:1 otherwise 7:7 52:9 139:13 191:15 OTIS 22:9 24:20 38:16 47:6 180:5 181:2 ought 159:9 163:17 164:9 165:3,4 ourselves 70:11,18 156:16 outcome 11:5 33:16 39:12</p>	<p>48:5,21 52:18 58:20,22 62:9 98:10 113:22 114:9,12 118:1,2,13,14,21 121:6 139:17 161:22 180:12 191:15 192:6 outcomes 11:2 13:7 21:2 33:1 41:19 48:8 49:20 56:5 58:10 62:21 72:4 73:21 95:18 98:16 117:17 118:13 119:15 123:5 142:15 149:20 150:7 151:5,9 157:19,22 158:1,11 163:19 164:12,14,15 170:18 outreach 15:16 22:19 outside 6:16,22 7:20 103:11 outstanding 100:14 ovale 75:7 overall 38:9 56:8 57:8,15 58:22 62:12 78:17 94:16 98:18 99:18 103:21 146:21 overcome 126:9 177:17 overcoming 165:11 overestimating 53:9</p>	<p>oversee 105:4 overseen 104:19 oversight 105:2 overview 110:7 overwhelming 155:8 <hr/><p style="text-align: center;">P</p><hr/>p.m 190:9 pack 81:4 package 16:16 114:22 154:15 paid 154:20 166:11 palate 78:20 Pamela 3:5 22:11 panel 4:16 5:17,18 8:7 16:12,16 41:8 42:2,7 67:6 83:20 107:1 123:15 130:12 146:5 panelist 189:18 panelists 2:2 18:13 19:20 26:6 91:17,22 92:9 146:22 paper 71:22 72:22 90:4 paper-based 125:14 Papillomavirus 38:17 parallels 167:21 parameters 79:21 parents 159:1 163:13 participants 25:4</p>	<p>50:12 participate 18:12 91:18 102:6 137:11 138:6 153:6,12 186:22 189:21 participating 98:8 107:18 189:19 participation 6:13 10:22 101:21 103:16 106:17 113:17 particular 32:20 94:4 96:20 108:18 109:18 110:2 114:20 122:16 139:12 141:15 174:5 particularly 44:6 62:12 84:20 86:14 144:15 146:4 176:1 188:7 parties 102:21 191:11,14 partly 157:5 partnering 124:7 partnership 174:17 175:4 party 192:5 passage 28:19 passing 175:13 passion 17:13,15 18:16 passive 40:4 113:1,6,15 121:10 149:3 past 89:18 97:21 104:2</p>
---	--	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 30

<p>Pasteur 5:15 20:15,16 113:20 115:8 121:17,19 122:17</p> <p>patent 75:6,7 184:1,7 187:2,8</p> <p>patience 148:22</p> <p>patient 24:14 96:5 106:1 114:14 116:2 117:20 120:20 121:2 125:16,18 128:8 130:9 139:16 140:13 145:16 179:20 180:6 182:5,14</p> <p>patient/physician 105:22</p> <p>patients 15:13 17:18 28:11 30:5,13 35:21 39:15 64:7,8,11,12,13 93:12 101:20 102:4 115:2,5 140:8 146:12,18,21 148:8 152:11 174:17 175:4 180:12,13</p> <p>patient's 140:1</p> <p>pattern 99:20 100:9 186:14</p> <p>patterns 106:1</p> <p>Paul 91:20</p> <p>pay 57:15 63:16 70:18 87:6,7 91:19 160:10</p> <p>paying 87:16</p> <p>PDA 75:12</p>	<p>pediatric 4:4 6:6 19:6 23:4,8,14 26:16 133:19 134:12 135:2 172:8,11</p> <p>pediatrician 20:10 23:10 76:9 82:11</p> <p>pediatricians 71:6 73:14 77:6 82:13</p> <p>pediatrics 5:8 22:8 73:16</p> <p>peer 38:10</p> <p>peer-reviewed 33:14 34:6,19 38:8</p> <p>peers 66:18</p> <p>Peggy 2:14 25:19,21 157:17 158:5,13</p> <p>people 70:2,4 75:10,19 80:18 81:1 84:11 87:4,7 88:16 91:3,6,11 126:1 137:10 148:1,5,11,19 152:9 153:7,10 156:16 160:14 164:9 174:13,20 175:8 188:17</p> <p>people's 153:13</p> <p>per 18:1 60:19 61:6,15,16 107:22 145:15</p> <p>perceive 180:15</p> <p>perceived 93:22 140:7 176:16</p> <p>percent 10:8 36:11,13,16,17,18</p>	<p>39:6,8,10,17,18, 19 59:1 60:18 64:11,12 69:15,16 70:3,5 71:1,8,11,15,22 72:3,8,15,16 77:11,12,14 78:16,17 81:7,13 98:3,5,11,13,14, 19,20 99:1,4,5 122:9,11,13 129:19 130:7 142:5 161:10 180:17,21,22 181:7 182:11,17</p> <p>performed 27:21 35:3</p> <p>perhaps 53:10 54:17 138:19 142:16 181:11</p> <p>periconceptional 144:11,14</p> <p>Perinatal 46:18,20</p> <p>period 9:17 10:7 18:17 35:7 52:21 118:11 122:7 133:19 149:16</p> <p>periodic 89:19 119:2</p> <p>Permanente 21:5 47:13</p> <p>permission 136:19</p> <p>person 6:13 55:22 56:21 60:4 153:5</p> <p>personal 170:17 180:16</p> <p>personally 152:8</p> <p>perspective 12:21 15:12 101:4 149:12 160:6</p>	<p>170:17,18 182:10 186:20</p> <p>perspectives 43:22 44:4</p> <p>perspectives/ challenges 4:18 16:14 43:13</p> <p>pertaining 50:19</p> <p>pertinent 178:17</p> <p>pertussis 140:5,6</p> <p>pharmaceutical 14:12 93:10 96:1 100:12 101:5 103:10 105:4 107:10 110:12 115:7</p> <p>Pharmacoepidemiology 5:3,15</p> <p>pharmacokinetic 28:2</p> <p>pharmacological 11:15</p> <p>pharmacovigilance 4:7 21:17 40:5 117:14</p> <p>Pharmacovigilance 22:22</p> <p>Pharmacy 21:6</p> <p>PharmD 2:19 5:14</p> <p>phase 120:7 149:3</p> <p>PhD 2:3,5,6,11,14 3:5,7 4:20 5:10</p> <p>Phenobarbital 85:6,9</p> <p>phone 25:7,9 43:9 115:1 116:1,14 189:12</p> <p>phones 6:21</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 31

<p>physician 25:12 130:10 180:7</p> <p>physicians 102:4 147:20 152:10 175:9 180:10</p> <p>physiological 75:8</p> <p>PI 25:1 64:16</p> <p>pick 146:9 159:9,11</p> <p>picked 133:5</p> <p>picture 109:3 110:3</p> <p>piece 138:12 158:7</p> <p>pillars 11:9</p> <p>pills 62:18</p> <p>pilot 129:18 130:5</p> <p>pinch-hitting 19:11</p> <p>places 175:16</p> <p>plan 104:4</p> <p>planned 108:1</p> <p>planning 6:8 29:12 104:5 105:15 106:18 125:4</p> <p>plates 180:11</p> <p>plausibility 120:5</p> <p>play 62:2 171:5</p> <p>please 6:20,22 7:11 8:9 82:3 84:1 91:19 131:14 138:3 154:4 171:9 190:5</p> <p>pleased 92:16</p> <p>pleasure 8:19</p> <p>plenty 82:12 109:1</p>	<p>plus 91:12</p> <p>PMC 36:9</p> <p>PMCs 124:1</p> <p>PMHS 4:5,10,13,21</p> <p>PMR 36:9</p> <p>PMRs 124:1</p> <p>podium 19:5 36:1</p> <p>point 68:3 72:5 74:12 75:14 86:6 102:2 124:16 127:18 143:18 144:4 145:20 150:10 161:14 164:7 184:6 186:3,6,16</p> <p>pointed 68:17 160:14</p> <p>pointing 173:5</p> <p>points 43:4 50:17 67:20 79:17 92:21 124:10 164:13</p> <p>policies 102:20</p> <p>polydactyly 73:15,17,18,22 74:2,10,13</p> <p>polytherapy 97:3,13 103:20</p> <p>pool 137:14</p> <p>pooling 47:13 101:7</p> <p>poor 45:10,13 75:11</p> <p>poorly 170:1</p> <p>population 11:7 63:1,4,6 72:14 79:16 86:7</p>	<p>94:3,7 95:7,19 96:5 97:5 128:19 137:4 172:16,20,21 173:2</p> <p>population-based 110:18</p> <p>population-specific 106:16</p> <p>position 29:8 156:13</p> <p>positive 89:16</p> <p>possibilities 147:22</p> <p>possibility 11:22 83:14</p> <p>possible 58:8 93:14 151:15,16 157:20 163:18 169:12</p> <p>possibly 150:12 153:18</p> <p>post 5:11 7:17 16:3 27:3 29:19 146:19 159:21 169:13 185:16</p> <p>post-approval 1:5 4:11 6:12 9:11,17 16:8 21:14 26:19 27:21 29:18 45:19 46:3 105:19</p> <p>postaxial 74:2,11</p> <p>Post-college 80:17</p> <p>posted 7:14</p> <p>posters 64:18</p> <p>post-market 10:7 28:13,15</p>	<p>post-marketing 10:3 28:22 35:16 123:16 167:16</p> <p>postpartum 50:3 159:5 181:13</p> <p>post-screen 57:16</p> <p>potential 11:16 30:10 48:16 51:7 53:6 63:16 94:14 100:10 104:1 114:1 120:11,12 123:1 137:14 144:7 152:22 154:16 159:8 178:8,19</p> <p>potentially 33:2 155:7 176:2</p> <p>power 45:2 58:20 59:6,14,21 78:12,16 101:18</p> <p>powered 162:7</p> <p>powerful 75:1 91:5</p> <p>powering 161:3</p> <p>powers 63:18</p> <p>practical 129:5 184:9</p> <p>practice 20:11 21:19 24:17 32:22 33:12 34:8 38:14 105:1</p> <p>practiced 23:16</p> <p>practices 15:16 106:9 116:22 152:14,16</p> <p>practicing 139:19</p> <p>practitioners 177:10,20 178:3</p> <p>pre 132:3</p>
--	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 32

<p>preapproval 45:7 preaxial 74:10 precedent 187:3 precise 121:9,12 precisely 138:15 preclinical 109:11 predict 86:3 145:1 166:9 predictors 45:11,13 predominant 82:2 preference 81:7 preferentially 55:1 144:16 preferred 106:6 pregnancies 10:9 54:10 61:10 81:10 98:11 116:13 140:22 141:4 167:17 170:10 172:7 pregnancy 1:5 4:11,17 5:8 6:12 9:11,13,20 10:11,12,15,17 11:5,10,18,20 12:4,8,9 13:1,3,5,7,21 14:5,7,9,17,20 15:2,6,9,14,17,2 0 16:7,9,13,21 17:20 21:2,11,15 22:4,10,18 24:1,13,20 25:16,17 26:11,18 27:6,7,20 28:7,17,19 29:3,4,7,8,10,16 30:1,6,8,19</p>	<p>31:1,2,19,22 32:3,8,18 33:16 34:2,7 36:5,19 37:1,2,4,6,8,11,1 3,19,22 38:2,4,12,18,20, 22 39:12 40:15,20 41:1,7,12,14 42:15,20 43:12,21 44:6,15,17 45:1,6,18,21 47:4,6,22 48:1,6,7,20 49:4,10 50:22 51:1,4,18 52:8,11,13 53:4,6 54:4,20 55:4 57:19 58:9 60:8 62:5,12 67:16 68:2,4,9,10 69:9 73:20 74:6 75:21 77:20,22 79:3 80:15,19 82:7,14 87:5,18 90:14 93:2,4,7,8,11 94:6 95:8,13,17 96:13,15 97:8,9,19 100:6 104:18 106:13 109:2,9 110:7,10,11,13,2 1 112:7,20 113:11,12,22 114:10,13 115:8,13 116:4,19 117:11,17,22 118:5,10,12 119:5,10,15 120:7,16 121:17,19,22 122:8,14,21</p>	<p>123:4,7 125:12 127:16,19 128:22 129:8 130:17 131:7,20 132:3,8 133:14,18 134:7,21 135:14,17 138:12,21 139:6,21 140:14,18 141:5,8 143:4 145:20 147:4,5 149:18 150:1 152:15 154:17 155:5,7,8 157:19 158:10,14 159:4 161:7,16 162:2,13 164:11,12,14,15 165:16 166:8,11,15 169:15 171:18 172:4 176:7,15 177:2 178:6,19 179:5 181:7,12 184:11 185:4,18,20 187:10,21 188:1 pregnancy-related 22:19 pregnancy's 96:11 pregnant 10:2,22 27:4,16,21 28:2,13,16 29:6,18 32:2 41:19,20 45:15 46:2 48:13 49:15,18 51:21 52:9 55:21 68:19 69:3 93:3 95:5 110:1 116:8 139:4 141:14 142:3 151:14</p>	<p>152:18,19 154:2 155:2 172:22 187:17 preliminary 27:13 67:2 premarketing 45:7 109:12 prematurely 74:22 prematurity 51:2 75:16 Prematurity- related 74:18 prenatal 50:11 53:4,17 54:2 58:5,16 75:21 82:5 83:9 114:9 132:2 172:9 preparation 30:20 prepared 19:16 110:5 192:3 prerogative 76:11 prescreen 57:3 prescreening 57:3,16 prescribe 147:20 177:12 prescriber 65:5 prescribers 15:13 17:19 181:9 prescribing 21:19 prescription 154:3 prescriptions 62:18 153:22 presence 64:21 present 18:14 27:6,12 56:7 60:7 62:15 75:20 92:13 108:19</p>
--	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 33

<p>presentation 12:17 13:10 16:10 44:8 56:3 62:4 67:11 92:6 93:16 107:3 108:17 146:13 166:9</p> <p>presentations 7:13 43:18 44:3 92:7</p> <p>presented 37:20 38:3,5 65:19 84:21 166:13</p> <p>presenters 4:16 5:17 7:14 42:6 123:14</p> <p>presenting 27:11</p> <p>pretense 80:16</p> <p>preterm 150:5</p> <p>pretty 36:9</p> <p>prevalence 30:9 58:22 98:18,22 99:3 173:6,16,18 174:9</p> <p>prevalences 59:3 172:2 173:11</p> <p>prevent 66:20</p> <p>preventive 25:12 137:11</p> <p>preview 44:2</p> <p>previous 162:10,15</p> <p>previously 140:17 190:4</p> <p>primarily 10:17 77:9 98:21</p> <p>primary 22:1 58:17 105:12 147:19</p> <p>prime 88:3</p>	<p>principal 25:15 49:8</p> <p>principles 188:12 189:9</p> <p>prior 11:14 113:11 142:8</p> <p>privacy 128:5,14 134:9</p> <p>private 105:1</p> <p>probably 47:9 74:9 75:18 86:6 127:5 130:1 141:12 159:13 169:5 181:2 185:7</p> <p>problem 53:6,7,21 77:17 142:12 154:10 162:22 177:17 178:5</p> <p>problematic 146:2</p> <p>problems 52:7 53:17 69:10 135:5 160:7 170:15 178:21 179:17 188:21</p> <p>proceeding 8:6</p> <p>process 68:18 69:7 82:22 85:12 112:11 122:15 126:5 132:17 148:18 158:21 166:17 184:15</p> <p>processes 102:19</p> <p>produce 165:5 184:2</p> <p>produced 156:5</p> <p>producing 184:4</p> <p>product 9:13 10:5 11:20 16:4 20:9</p>	<p>33:6,8,21,22 34:17 35:12,14 40:6 41:16 92:19 94:1,2,12,15,18, 20 95:1,3,4,6,7,9,12 97:3 101:1 105:20,21 107:7,21 117:15 118:8 127:11 183:5,8</p> <p>products 1:5 6:11 9:10 10:7,11 14:20 18:1,9 27:18 31:1 32:1,10,13,14 35:15 36:5,11,13,16,21 38:6,9,13 39:3,7,13,16 40:11 91:1 93:10 94:11 95:2,14,22 96:3,20,22 97:12,15 108:3 184:14 185:16 187:1</p> <p>product-specific 18:2,10 107:12</p> <p>professional 28:10 115:17,18,20</p> <p>Professor 5:4,8 23:20</p> <p>profile 10:4,19 14:19 93:10 96:4</p> <p>program 5:4 13:6,11 22:4,16 24:5 71:3,21 84:10 170:3 171:8,15 178:18</p> <p>programs 13:4 51:3 129:19 149:4</p>	<p>168:1,6,7,13,15, 20 169:5,18</p> <p>project 4:3 6:4 23:7 31:17 46:19,20 69:13</p> <p>projects 21:1 47:14</p> <p>prominent 29:8</p> <p>promoting 176:7</p> <p>promotional 176:3</p> <p>prompting 154:9</p> <p>proper 129:1</p> <p>proportion 36:8,9 65:1,7</p> <p>proportions 34:14</p> <p>proposal 72:13</p> <p>proposals 160:17</p> <p>proposed 29:1</p> <p>proprietary 103:7</p> <p>Proquad 37:5 38:21</p> <p>prospective 11:2,6 48:2 50:10,12 62:6 98:2,10 113:8,9 114:10 131:19 132:1,6 133:1,20 135:8 138:10 139:11,20</p> <p>prospectively 113:10 114:5 119:12,14 120:2 133:9 139:16</p> <p>protease 183:16,21 184:4</p> <p>protect 140:4</p> <p>protocol 39:4 70:18</p>
--	---	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

<p>protocols 33:19 129:17 160:16</p> <p>provide 8:7 15:12 27:5 30:2 43:19 45:22 46:1,5,6 63:14 93:9 102:9 105:1 109:13 112:3 145:9</p> <p>provided 11:13 31:3 34:8 112:12 121:2</p> <p>provider 101:21 114:15 116:7,8 117:19 120:21 121:3,5 125:16,17 128:8 182:6,7,13,14</p> <p>providers 14:14 28:10 30:12 93:13 101:5 102:5 115:2 116:3,17</p> <p>provides 100:3</p> <p>providing 55:10 102:6</p> <p>provoked 144:3</p> <p>psychology 158:18 159:20</p> <p>public 1:8 5:4 6:9 7:4,12 8:20 14:13,14 16:18 17:4 18:14,17 23:21 27:22 28:7 29:13 30:20 66:18 86:19 115:21 145:11,17 163:18 186:3,15 190:1,10</p> <p>publication 33:13 71:12 73:22</p>	<p>publications 34:6 142:20</p> <p>publicize 42:14 65:21</p> <p>publish 37:14 61:21 78:5,9 84:22 85:21 88:5 90:15 134:22 142:17</p> <p>published 10:15 24:10 28:16 29:2 34:18 35:9 38:8,10 40:1 41:4 70:14 71:5,22 72:22 100:2 112:6 130:3 168:21 173:19</p> <p>purchase 8:4</p> <p>pure 50:10 133:1 135:8</p> <p>purely 172:16 186:15</p> <p>purpose 9:3 33:3 93:8</p> <p>pushed 175:3</p> <p>puts 78:21</p> <p>putting 108:21 168:16</p> <hr/> <p style="text-align: center;">Q</p> <hr/> <p>Q&A 5:18 130:12</p> <p>QIV 111:14 121:21 125:22</p> <p>Quadrivalent 38:17</p> <p>qualifies 132:6</p> <p>qualitative 75:14 119:22 163:3</p>	<p>166:4</p> <p>qualities 70:1</p> <p>quality 24:3 34:21 40:16 74:16 76:5 167:19 168:17 179:12</p> <p>quantitative 120:1</p> <p>question 10:19 64:4 66:2 67:6 78:4 84:15 88:19 89:4,12 90:19 122:22 129:16 130:18 131:3,19 134:6 138:8 139:22 140:14 144:20 149:9 150:13,16 160:15 165:8,22 171:6 177:5 178:17 181:2 183:3,18 187:9</p> <p>questionnaire 117:18 118:5 125:15</p> <p>questions 4:16 5:17 7:2 16:16 42:1,3,5 43:9 50:3 67:10 83:20 84:21 88:8 91:20 92:8 106:22 123:11,13 130:15 151:12 157:4 159:9 174:5</p> <p>quick 109:7 110:3</p> <p>quite 22:4 25:10 59:15 61:6 97:10 147:7 154:7 156:3,12</p> <p>quote 162:15</p> <p>quoting 162:12</p>	<hr/> <p style="text-align: center;">R</p> <hr/> <p>raise 57:3 177:4 178:7,12</p> <p>raised 65:13 145:1</p> <p>random 51:15 80:19</p> <p>randomized 154:22</p> <p>range 39:18,19 150:6 169:6,12 180:21 184:22</p> <p>ranges 98:20</p> <p>rare 35:13 145:7,8,10 146:10 170:8,21</p> <p>rarer 146:4</p> <p>rate 39:15,17 71:1,7,15,21 72:7,13,19 73:12 77:11,12 81:3,8 86:3,7 89:10 126:5 130:6 141:18,19 142:6 143:1 159:12,13 180:20</p> <p>rates 56:19 120:9,10 128:21 144:16 156:3 180:17 182:20,21</p> <p>rather 61:2,16 70:20 82:4 126:20 127:20 134:16 167:15</p> <p>ratio 56:20</p> <p>rational 15:14</p> <p>reach 147:22</p> <p>reached 34:20</p>
--	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 35

<p>91:15 reading 76:6 123:21 ready 88:3 160:4 186:10 190:6 real 16:14 55:2 60:6,22 62:18 91:11 139:19 147:9 156:4 157:21 158:17 164:2 172:2 187:9 realistic 87:17 141:8 149:12 150:10 160:8 182:18 reality 16:2 59:17 60:4 80:21 134:21 135:14 realized 106:4,19 really 8:20 9:12,14,17,20,22 12:12,22 13:19,20,22 14:2,5,6,8,14,16, 18,21 15:3,5,22 16:6,8 17:5,11,18 18:3,11 19:16 26:7 67:20 70:5 73:18 78:22 82:7 87:14 91:5 108:21 130:15 132:21 133:1,19 134:19 136:16 137:6 142:6 144:7 148:3,7,17 149:5 153:9,10,12 158:1 161:14 162:7 164:18,21 166:1,16</p>	<p>175:17,18 176:5,11 178:7 183:3 184:13 187:18 188:18 real-world 93:4 reason 11:22 138:2 reasonable 149:16 162:13,20,21 163:16 180:19 reasoning 157:8 reasons 32:12 39:9 134:15 151:20 173:11 reassurance 90:8 reassuring 145:22 rebate 154:18 recall 62:8 130:4 154:10 receive 114:6 118:3 received 29:13,14 122:8 receiving 48:3 153:22 recent 109:21 183:15 recently 27:8 137:16 183:14 recognize 28:1 51:21 162:19 recognized 10:12 65:21 72:10 100:11 172:13 recognizes 8:11 recommend 58:7 109:21 181:9 recommendation</p>	<p>153:18 recommendations 17:7 28:18 34:8 48:18 109:21 165:10 167:3 recommended 48:19 49:1 158:18 188:1 record 77:4,18 92:3,4 181:3 182:9 191:8 recorded 77:5 117:12 191:6 records 13:9 47:12 49:21 83:2 134:12 135:2,10 172:8 181:20 recruit 69:2 recruited 67:22 79:11 159:7 recruitment 69:6 106:10 114:18,19,21 115:5 155:15 176:19 recurring 136:21 red 54:5 61:9 reduce 101:19 reduced 150:3 191:7 refer 80:6,11 142:19 169:15 reference 11:7 48:10 49:17 51:14 53:22 54:7 57:21 58:13 161:11 171:16 references 33:11 90:3</p>	<p>referrals 82:2 referred 51:22 80:12 84:17,18,22 109:8 110:9 112:20 134:9 referring 104:13 refers 50:10,12 refreshments 8:4 regard 94:6 104:3 106:6 127:15 134:9 regarding 16:21 28:18 34:1 48:18 102:10 103:16 146:14 regards 176:3 regimens 97:2 region 96:21 regions 128:20 register 40:4 95:17 142:1,8 registered 7:9 190:2 registers 110:18 registration 7:3,5,6 91:21 153:19 183:20 190:5 registries 4:11,17 5:9 10:16,18 11:1 12:8,9,15,20 13:22 14:9,18 15:2,7,9,18 16:2,7,10,13,22 21:15 22:10 24:7,9,12,13,14 26:11,18 27:6,8</p>
--	--	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 36

28:19 29:17	165:10 166:2	96:2,6,8,14,16,2	registry/
30:2,22	167:12 171:18	1 97:9,11,20,21	pregnancy
31:3,20,22	172:4 173:7,14	98:1,4 100:6	109:11
32:4,8,12,13,15	174:3,14	101:4	registry-based
33:16	175:12,14	103:5,12,13,21	72:2
36:6,8,10,14	176:14	104:11,13,19	registry's 39:12
39:14	185:13,20 186:4	105:5,6 106:13	regression 56:12
40:10,12,15	registry 5:8 11:10	107:15 108:2	regular 112:13
41:2,7,13,15	13:1 14:7 15:20	109:9,11	126:2
42:10,13	21:11 22:18	111:1,2,3,7,13	regulated 28:8
43:12,21 44:6,15	24:14	112:4 113:14	regulations 118:18
45:1 47:4,6	25:15,16,17	114:7,12 116:4	128:5,14 154:20
48:1,2,12 49:1,5	28:17 29:7,11	117:4 120:17	regulators 14:12
50:20 51:4 57:18	30:6,8,12,14,19	121:22 122:21	101:6
62:6,22 63:7	32:18	123:3 125:4,13	regulatory 4:3 6:4
68:2 69:9 73:20	33:2,5,12,13	127:2,8,16,19	15:12 27:3 28:12
79:3 89:8	34:7,16,18,20	130:17 131:7	36:10 103:10
92:14,15,19	35:6,8,13,14,20,	132:9 134:22	105:6,19
93:4,9,18	21 36:11,15,19	137:15 138:13	106:8,15 111:20
94:6,12,17 95:1	37:1,2,4,6,9,11,1	140:18 141:6,8	119:1 127:10
96:10,19 97:7	9,22	144:22 145:4,20	145:17
100:10,21,22	38:2,4,6,10,12,1	147:4,6 148:7,13	Reilly 69:13
101:2,9,14,19	9,20,22 39:6,7	149:15	reinforce 144:3
102:3,13 103:17	40:16,18,21	150:14,18	187:6
104:6 107:6	41:11	152:7,11	related 21:2 53:20
109:2	42:11,12,18	153:5,21	78:4 92:9 93:1
110:7,10,14,21	44:17	155:5,8,11,19	131:19 191:10
111:6,11,12,18	49:7,10,13,19	156:5	relates 134:8
112:1,8,14,20	50:9,21 51:15,22	157:6,10,13,19	Relating 4:18
113:5 114:4,17	53:2,9,12,16	158:14 159:4	43:13
115:8,13,16	54:9,18,20	161:16 162:13	relation 62:13
119:11	55:4,7,20 56:6	164:8,11,16	relationship
121:17,20	57:17 59:11,20	165:16	180:6,15,16
122:17,18	60:8,11,13,14,20	166:4,8,11	relative 56:17
123:7,19 128:3,6	62:20 64:8,17	173:13 174:11	57:7,12 59:8
130:21 131:20	65:4,10,11 67:16	175:6 176:6,16	62:16 66:16
134:8 135:14	68:4,9,11 76:2	177:1,4	191:13
137:6 138:14	77:22 80:4,15,19	180:13,14,15,20	relatively 62:14
140:15 141:12	81:22 82:7,15	181:7	133:10,14
142:11 149:18	83:16 84:1,13	182:3,5,19,21	
150:1,19	87:6,18 89:2	183:6,9,13	
151:16,17 152:5	90:14 93:14	184:3,8,12	
153:9,19 156:20	94:2,7,15,19	185:4,6,18	
157:1,21 158:10	95:11,13,22	187:10,21 188:2	
161:7,9 162:2			

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 37

<p>147:12 179:5 release 85:4,17 86:15 87:3 135:20 136:14 156:1 released 85:5,10 releasing 85:7 relevance 94:6 103:12 relevant 52:20 151:11 reluctance 177:16 rely 63:8 75:10 remain 135:14 remained 84:4 remaining 39:16 remains 123:7 remarks 4:9 9:3 19:5,10,17 remember 8:9 51:20 68:5 reminder 131:13 remodeled 185:21 REMS 35:18 rent 160:10 repeatedly 163:13 replicate 66:6,19 report 66:6 90:1 105:9 110:5 112:18 115:3,15 116:2,3,14 118:18 123:19 124:12,22 125:18 126:3 129:8,11 130:10 150:14,15 reported 1:19 50:7</p>	<p>77:8 99:21 108:2 117:7,13 119:1,8 120:2 135:2 177:2 reporter 117:19 120:20 191:1,2 reporting 1:20 101:4 102:5,7 104:8 105:6 112:15 113:18 116:5,6 118:12 119:2 121:11 124:12 179:12 reports 33:19 40:3 46:3 73:13 98:4,10 100:3 116:10,16 117:4 122:8,9,10,11 129:7 179:1,10,11 repository 179:4 represent 14:14 51:12 54:4 representative 5:16 32:6 63:1,5 108:9,15 172:21 representatives 2:18 3:3 87:21,22 88:2 105:3 represents 51:12 55:5 60:10 61:8 186:12 reproductive 12:3 30:10 93:8 95:6,20 request 10:17 11:10 requested 29:19 requests 68:6</p>	<p>require 9:19 11:14 12:5 28:21 102:15,17 104:6 127:17 182:12 required 29:19 35:17 56:6 123:17 172:14 186:22 requirement 29:20 35:16 123:19 124:16 requirements 124:12 requiring 12:1 research 4:5 5:12 6:5 21:1,5,14 22:2,12 23:21 24:3 25:13 30:15 46:14 47:8 68:21 73:7 82:16 92:13 105:15 107:14 110:15 136:12 researchers 14:12 28:9 34:10 reservations 156:9 resident 172:18 resource 101:10 102:3 159:8 resources 30:17 40:18 47:14 66:19 101:7 127:18 138:4 160:4 respect 14:18 102:21 133:22 respond 151:11 responding 149:9 response 143:1,5,9 responsibility</p>	<p>41:21 responsible 103:4 105:7 107:16 110:13 187:15 restrict 57:2 restricted 12:22 Restrooms 7:20 result 41:11 49:4 52:2 54:22 56:22 94:14 117:4 189:6 resulted 34:16 results 27:7,13,14 32:20 33:6,13 34:7,18 36:2 38:7,10 57:4,10 58:2,4 83:4 89:15,17 90:16 97:19 112:18 134:22 135:1 resume 92:1 190:1 retention 16:1,21 retrospective 113:8 172:6 retrospectively 114:6,11 119:13,21 120:2 return 162:11 review 27:7,11 30:21 32:11 39:21 40:8,9,13,14 41:1 62:4 100:5 103:22 105:2 173:17 178:19 reviewed 38:11 117:14,16 reviewer 26:15 112:2</p>
--	---	--	---

Capital Reporting Company
 Food and Drug Administration Public Meeting 05-28-2014

<p>reviewing 92:20 172:8</p> <p>reviews 33:20 99:22 107:20</p> <p>revising 29:14</p> <p>revisions 29:12</p> <p>revisit 185:11</p> <p>ribavirin 95:12,15 183:13,15,17,20 184:1,5</p> <p>ride 81:12</p> <p>risk 5:15 13:5 22:16 35:18 37:17 41:13 48:16 56:11,14,17,19,20 0 57:7,8 59:8,10,15,18 60:21 61:5,7,9,15,16,18 8 62:16 66:16,17,22 85:14 87:4 93:1,10 95:8,9,12 96:4 99:7,18 102:10 109:17,20 144:7,18 145:13 150:3,4,21 155:7 156:15 178:8,12</p> <p>risks 53:9 57:12 145:6 152:21 153:1,4 156:8 164:1</p> <p>roadmap 44:20</p> <p>robust 101:22</p> <p>role 157:1</p> <p>roles 101:11</p> <p>room 1:16 7:21 31:6 41:5 88:17</p>	<p>166:1 188:9 189:21</p> <p>roughly 71:11,15 72:8</p> <p>round 44:4</p> <p>routes 94:21</p> <p>routine 48:4 90:12 108:1 124:4</p> <p>rule 29:1,5 37:13,14 170:4</p> <p>run 21:17 87:3</p> <p>running 9:1 64:3 66:15 182:21</p> <p style="text-align: center;">S</p> <p>safe 17:19 140:2 175:10</p> <p>safety 1:5 6:11 9:10,13,15 10:4,18 11:17 13:4 14:5,19 16:5 20:9 23:22 27:20 28:6,21,22 29:22 31:1 32:1 34:1,3 41:2 45:5 93:1,6,10 95:12 105:22 109:12,13 114:1 117:15 119:2 124:8 127:15 145:6 146:19 150:21</p> <p>Sahin 3:11 4:13 12:17 23:13,14 26:14,21 31:14,16 36:2,4 42:4,21 83:21 109:8 171:6</p> <p>sales 187:11</p> <p>sample 32:3,5 47:1</p>	<p>50:14 51:16 60:10,13 61:5 78:10 80:19 127:5,7 135:7,11 140:16 141:7 155:18 159:6 160:13,17 161:19,20 162:2 170:16</p> <p>San 22:7 25:11</p> <p>Sandy 19:12,15,18</p> <p>Sanofi 5:15 20:15,16 113:20 115:8 121:16,18 122:17</p> <p>sanofipasteurpreg nancyregistry.c om 115:9</p> <p>SARAH 192:2,11</p> <p>SAS 35:4</p> <p>satisfaction 106:1</p> <p>satisfying 105:19</p> <p>saw 83:3 86:2</p> <p>Scandinavian 110:19</p> <p>scant 9:14</p> <p>scaring 87:4</p> <p>scary 86:7</p> <p>ScD 2:4,19 5:14</p> <p>scenario 95:21 96:18 185:6</p> <p>School 5:4,8 21:6 23:21 86:19</p> <p>science 17:12 24:9</p> <p>Sciences 21:7</p> <p>scientific 84:3 85:2 86:22 88:15 104:21</p>	<p>105:2,13,16,20 106:4 129:6 183:12</p> <p>Scott 3:5 22:11</p> <p>screen 133:13</p> <p>screening 53:4,18 54:2 57:12 58:16 76:1,6 82:5 83:9</p> <p>screens 58:6</p> <p>screenshot 32:16</p> <p>scrounging 178:22</p> <p>SCS 144:15</p> <p>se 18:1</p> <p>search 33:17</p> <p>searched 34:4</p> <p>searching 65:3</p> <p>second 13:11,20 14:21 51:18 61:11 85:9 98:13 99:6 114:16 115:4 131:3</p> <p>secondary 49:3</p> <p>section 29:9 37:20</p> <p>sections 37:17</p> <p>seeing 132:8 142:4,6,18</p> <p>seemed 152:3 188:16</p> <p>seems 145:18 155:8</p> <p>seen 47:10 73:21 74:14 113:5 131:22 137:6 156:3 173:11 174:9,11</p> <p>sees 136:4</p> <p>seizure 80:10</p>
---	--	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 39

<p>selected 31:19 32:3 62:10</p> <p>selecting 53:16 54:22</p> <p>selection 50:18</p> <p>selective 63:17</p> <p>self 168:19,21</p> <p>semiannual 100:1,3</p> <p>semiannually 107:20</p> <p>send 88:5 148:10 181:17</p> <p>sending 125:15 147:16,19</p> <p>senior 4:3,21 21:13 23:3,7</p> <p>sense 55:18 63:1 159:7 185:6 186:17</p> <p>sensitive 58:3,5</p> <p>sensitivity 49:2 103:7 106:2</p> <p>sent 64:19 117:18</p> <p>sentinel 141:11</p> <p>separate 88:14 99:13 124:11 189:20</p> <p>separated 119:13</p> <p>separately 49:2 67:17 80:5 87:19</p> <p>separation 105:13</p> <p>septal 75:13 79:18 80:2</p> <p>sequentially 185:10</p> <p>series 40:3 43:18</p>	<p>46:4 179:12</p> <p>serious 11:17 119:7</p> <p>seriously 125:21</p> <p>seriousness 119:6</p> <p>serve 6:4 102:3</p> <p>served 44:1</p> <p>Services 5:11</p> <p>serving 107:14</p> <p>session 5:19 17:5 130:14 188:3,5 190:2</p> <p>setting 1:5 6:12 9:11 89:15 93:4 126:18,20,22 127:2 135:15</p> <p>setup 103:4</p> <p>seven 36:20 38:6,13 50:1 181:12</p> <p>Seventeen 39:8</p> <p>Seventy-eight 98:3</p> <p>Seventy-six 36:11</p> <p>several 11:11 30:4 34:15 68:11,18 69:14 71:12 94:11 102:12 117:21 160:14 176:19 181:12 185:15 186:5</p> <p>severe 118:15</p> <p>severity 81:11</p> <p>shadow 162:14</p> <p>share 6:19 92:18 167:20</p> <p>shared 41:20</p> <p>sharing 107:11</p>	<p>shoestring 148:21</p> <p>short 63:12</p> <p>shot 168:3</p> <p>showed 70:5 73:7 76:22 86:17 142:21 155:20</p> <p>showing 71:15 86:9</p> <p>shown 81:17 181:4</p> <p>shows 75:6</p> <p>shy 165:21</p> <p>sick 179:21</p> <p>sight 149:18</p> <p>sign 7:5 80:18 83:1 134:11 136:7,14 148:8 177:21</p> <p>signal 114:2 120:11,12 122:21 141:16 146:21 162:4</p> <p>signals 46:5 114:1 123:1</p> <p>signature 135:20 136:10</p> <p>signed 84:16 136:2</p> <p>significance 73:5 74:16</p> <p>significant 6:16 76:17,18 78:7 80:17 81:1 90:10 99:7,18</p> <p>silence 6:20</p> <p>Silver 1:17</p> <p>similar 36:9 56:22 67:19 72:4 96:4 108:19 109:10,14 110:5 112:10,11</p>	<p>115:10 135:4 150:19 151:2,8 167:8 169:13 173:12</p> <p>simple 56:11 95:21 189:8</p> <p>simply 163:11</p> <p>sincerely 6:14</p> <p>single 93:17 94:14,18,19 95:1 96:1,3 97:14,20 101:1 102:7 111:1,3,7 153:2 179:11 183:7 189:7</p> <p>Singulair 37:3</p> <p>sit 129:6</p> <p>site 76:4</p> <p>sites 172:9</p> <p>sitting 74:15 82:12</p> <p>situation 53:19 54:5 56:2 161:15 179:1 185:11</p> <p>situations 185:3</p> <p>six 20:17 38:8 40:9 84:10 112:12 122:7 158:19 159:7,15,21 160:5 163:9 173:4</p> <p>size 42:12 47:1 60:10,13 61:5 78:10 79:21 80:3 127:5,7 135:7,11 140:16 141:7 144:21 145:2 146:1 155:18 159:6 160:13,17 161:19,20 162:2 164:8 170:16</p>
--	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 40

<p>skilled 83:7</p> <p>slam 185:5</p> <p>slide 7:13 38:5 40:8 70:5 75:6 80:8 86:2</p> <p>slides 63:20 67:17 90:4 108:21 109:5</p> <p>slightly 72:11 109:3</p> <p>slippery 139:14</p> <p>Slone 24:22 47:20</p> <p>slope 139:14</p> <p>slower 132:17</p> <p>slowly 111:12,17 125:8</p> <p>small 46:22 62:2 81:3</p> <p>smaller 162:3</p> <p>smallpox 25:16 137:8</p> <p>Smartphone 125:20 129:17</p> <p>Smartphones 126:1 137:17</p> <p>Smith 69:13</p> <p>smoking 50:6 81:3</p> <p>snapshot 150:2</p> <p>so-called 50:11</p> <p>society 80:16,20 147:15</p> <p>solely 157:6</p> <p>solicitation 154:14</p> <p>Solomon 3:6 4:7 8:16 22:20 42:3 162:10</p>	<p>solutions 131:9</p> <p>solved 163:7</p> <p>somehow 66:18 134:17 135:22 185:20</p> <p>someone 74:13 82:10 83:6 134:14 137:19</p> <p>somewhere 159:15</p> <p>Sonia 2:12 5:3 23:19 44:8,10 65:18 67:15 68:17 69:18 70:5 78:13 80:8 81:17 83:7 86:17 90:4 186:1</p> <p>Sonia's 86:2 132:20</p> <p>sonographer 133:13</p> <p>sooner 148:14</p> <p>sophisticated 86:18,21</p> <p>sorry 129:4 158:8 183:10</p> <p>sort 9:5 12:21 13:2 17:15 18:22 72:11 91:2 107:4,8 132:1,18 139:14 150:2 152:13 160:18 161:2,3 164:19 165:2 166:3 167:14 169:7,13 178:14 185:5 188:17</p> <p>sound 126:10</p> <p>sounds 64:6 149:2 152:6</p> <p>source 82:2 86:12</p>	<p>116:6 123:8</p> <p>sources 34:5 41:12 47:7 71:16,18 106:3 110:9,16 112:15 116:6,20 156:22</p> <p>South 21:7 127:13</p> <p>spanned 57:19</p> <p>spanning 160:19</p> <p>speak 7:8,9,10 8:10,11,13 20:2 44:9 79:4 92:17 107:6 108:9 124:10 131:14</p> <p>speaker 7:5 8:7,16 19:3 26:13</p> <p>speakers 7:4 16:15</p> <p>speaking 8:12 142:21 190:5</p> <p>speaks 143:15</p> <p>special 93:20 104:3</p> <p>Specialists 38:16</p> <p>specialty 172:11</p> <p>species 45:13</p> <p>specific 16:20 18:1,9 44:22 46:21,22 47:2,3 49:6 55:15 57:22 58:15 59:2,7,19 63:3,18 65:7 69:22 73:11,19 79:5 88:22 99:20 100:7 104:15 107:8,22 117:3 120:22 143:2,11 146:3 151:13 161:5 162:8 174:7</p>	<p>specifically 17:8 44:3 46:17 47:8,17 55:11 65:15 106:9 109:18 121:2 130:21 138:21 170:6,14</p> <p>specified 11:1 35:2</p> <p>spectrum 14:15 80:16 149:20</p> <p>spend 82:8</p> <p>spent 65:10 138:4</p> <p>spina 89:6</p> <p>sponsor 98:1 105:3 184:3 187:16</p> <p>sponsors 10:18 12:6 87:21,22 88:2,6,14 105:11</p> <p>spontaneous 56:4,7 58:1,11 113:17 118:16 119:16 121:11 122:9 150:5</p> <p>spread 184:18</p> <p>spreading 148:18</p> <p>Spring 1:17</p> <p>spurious 156:11</p> <p>Sr 5:11</p> <p>SSRIs 178:10</p> <p>stable 172:1</p> <p>staff 4:4 6:7 19:7 23:5,8,15 26:15,16 33:20 82:21</p> <p>stakeholders 14:15 41:21 101:8 103:14</p>
--	--	--	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 41

<p>104:14 106:17 stand 81:14 standard 142:11 169:7,17 standardization 101:16 standardize 28:14 standards 168:12,17 169:2,4,13 standpoint 135:6 177:15 stands 81:14 start 19:22 20:1 27:10 44:7 70:10 108:14 113:10 128:20 148:17 149:6 166:22 183:19 started 24:14 35:8,10 60:14 74:19 78:1 82:9 111:13 121:22 133:6 136:11 137:8 138:9 168:8,16 starting 16:8 32:9 112:14,19 state 8:13 84:13 131:14 146:11 154:11 168:1 188:8 stated 33:8,9 39:3 statement 100:3 States 35:22 68:20 95:16 111:15,20 126:12 127:3,12 132:9 statistical 101:17</p>	<p>104:8 135:6 statistically 99:18 105:9 statistician 22:14 statistics 34:12 status 4:12 15:6 26:19 27:5 29:16 39:6 44:5 135:17 stay 163:12 steadily 86:3 steady 6:10 86:12 steering 100:16,18 104:19 step 18:16 72:12 106:15 170:13,16 stepping 19:8 175:19 steps 17:7 68:18 stillbirth 118:16 119:17 stops 89:2 stories 90:8 story 75:15 straight 173:22 straightforward 188:14 Strategic 5:11 strategies 15:8 18:22 41:6 106:7 strategy 35:18 90:21 93:15 stratified 34:14 streamline 101:20 stressing 81:21 striving 169:9</p>	<p>182:17 strong 59:15,17 strongly 187:22 struck 177:1 structural 72:6 structure 83:22 100:17 104:12,18 105:12 107:4 struggle 136:7 140:20 176:22 stuck 19:13 studies 4:12 10:17 11:14 12:1,6 21:15 24:20 26:19 28:22 30:4 40:2,3 45:8,11,19 46:8,14,15,16 47:7,16 62:7 70:10 71:14 72:4,21 75:2 113:7 116:21 117:2,3,6 122:12 123:2,4,17 142:8 145:9 146:17 157:2 158:15 studying 52:6 58:10 62:13 stuff 140:2 143:14 154:2 168:15 175:12 stumbling 176:4 subdivide 83:8 subject 9:4 178:7 subjects 53:3,5 54:1 58:17 59:13 submit 7:11 37:15 88:7 100:15</p>	<p>submitted 67:18 submitting 72:13 subtle 85:15 subtract 71:9 72:9 success 16:1 42:17 104:10 107:6 140:17 successes 12:10 15:7 31:7 successful 12:14 30:7,18 40:17 41:11 successfully 153:21 Suddenly 77:13 sufficient 41:15 59:14 99:11 108:5 145:4 166:11 suggest 100:9 177:16 suggested 185:19 suggestion 167:2 185:17 suggestions 14:11 131:9 suggests 41:1 suites 189:4 Sumatriptan 96:13 summarize 100:5 summary 27:12,15 37:17 41:14 56:19 57:17 82:6 83:11 122:20 supervises 68:1 supplements</p>
---	--	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 42

<p>144:10 support 88:20 184:17 supported 78:2 supporting 57:14 supposed 139:21 154:1 sure 19:19 52:22 78:5,9 84:2 130:2 132:22 135:17 155:4,14 160:8 165:16 171:12 182:11 surgery 172:14 surgical 72:6 surveillance 4:8 21:1 27:10 40:5 46:4 47:19 71:3 110:18 113:1,4,7,15,16 116:22 117:3 121:10 123:17 124:4 130:5 168:5 169:3,14,16 surveys 147:10 surviving 75:1 Susan 2:4 21:22 suspect 134:7 136:1 suspected 43:5 suspicion 135:21 swing 138:8 switched 165:8 sworn 191:5 symmetrics 15:22 system 17:10 22:10 25:2 69:12</p>	<p>72:3 74:6 82:15 113:19 121:10 125:11,19 155:3 160:1 162:20 164:19 172:13 177:14 systematic 32:11 40:9 76:1 90:11 systems 17:17 18:5 30:18 46:5 47:19 119:3 124:12 132:17 160:20 161:2,5 177:3 T table 7:5 60:10 78:13,22 103:3 134:6 tables 6:22 7:3 tabulations 79:15 take-home 79:2 taking 54:19 69:4 70:15 80:10 111:16 115:13 117:2 132:4 141:5 143:20 147:11 154:2 178:13 talk 12:16 13:14 27:1 49:12 50:17 64:5,9 74:9 83:21 88:4,22 89:5 100:19 124:20 134:13,14 136:13 144:5 145:20 153:17 162:12 178:4,6 talked 16:11 79:18 talking 12:18 13:21 18:1,3</p>	<p>59:3,9,19 68:22 72:5 73:14 82:8 86:9 143:3 144:6 145:15 146:15 160:11 161:18,20 165:12 174:19 175:10 talks 115:21 target 33:9 34:20 39:2,3,4 132:2 134:1 138:11 task 178:15 Tassinari 3:7 4:20 23:2,3 43:2,10,16 63:22 64:2 65:13 67:5 83:19 90:18 91:14 92:1,5 106:22 108:7 123:11 125:2 126:10,21 129:3 130:13 136:22 138:7 140:9 149:2 157:14 158:5 165:6 171:4 176:18 179:22 180:19 183:1 188:4 189:11,15 190:8 taught 70:4 Tdap 109:22 team 31:8,17 34:22 82:10 technologies 132:13 technology 24:4 75:22 134:2 teeth 167:3 telephone 3:13</p>	<p>25:4,19 69:1 ten 20:10 29:11 137:9 tend 53:11 55:17 132:12 tenofovir/ emtricitabine 36:22 teratogenesis 188:12 189:10 teratogenic 81:11 179:3,19 teratogenicity 45:9,12 teratogens 149:21 160:22 teratology 38:15 189:2 term 94:18 138:10 162:14 176:20 termination 54:17,21 119:17 terminations 51:5 terminology 68:6 terms 10:1 12:14 26:10 30:14,16 36:19 39:2,6 61:8 62:1 76:4 78:8 107:5,11 126:13 129:13 134:4 136:9 141:2 144:21 145:16 161:3,6 162:3 164:7,18 167:4 territories 98:5 test 50:11,14 53:6 tested 162:6 testimony</p>
--	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 43

<p>191:4,6,9 tests 114:9 Thalidomide 59:10 146:1 165:1 170:3 Thalidomides 164:20 170:2 thank 6:15 19:8 20:12 21:8 22:5 23:17 25:9 26:6 31:14 36:3,4 41:22 42:21 43:1 44:13 63:20,22 67:12 83:17 91:14,22 92:14 106:20 107:2 108:11,15 123:9 131:17 138:7 171:11 188:4 189:14 190:8 thanks 19:9 20:18 that's 11:5 15:18 51:11 52:12,18 56:1 60:18 61:1,20 65:3 66:1,12 72:1 77:15 89:3,7 91:12 125:19 127:21 133:13 134:21 140:11 150:9,12 151:5 155:4 157:5 161:13 163:4 166:5 171:15 178:14 184:22 187:18 188:18 themselves 8:9 19:21 41:15 116:9 168:13,15 169:11 theoretical 109:17 147:22</p>	<p>theoretically 159:6 theory 55:2 therapeutic 102:18 106:11 187:4 therapy 94:10 99:10 thereafter 191:7 therefore 58:6 62:7,15,17 63:3,11 184:3 there's 67:7 73:17 132:17 139:2 142:10 148:2 166:10 179:3 they're 9:22 72:22 126:13 134:16 137:21,22 149:19 152:6 174:4 they've 169:10 third 24:10,12 51:18 98:15 99:6 116:5 134:10 135:7 136:18 Thirty-nine 98:12 thorough 116:14 thoughtful 131:8 thoughts 126:13 130:19 146:7 153:14 165:14 171:10 179:22 188:7,9 thousand 86:5 thousands 78:22 79:8 87:16 148:12 threefold 57:8 threshold 99:13</p>	<p>107:21 108:4 throughout 57:19 68:19 161:17 throw 148:12 187:14 thumb 74:11 ticking 136:9 timeframe 173:7 timeline 28:12 timelines 102:20 Tina 22:6 131:18 138:9 140:9,10 144:22 149:7 164:13 176:9 180:3 tire 19:14 tissue-fluid 133:11 Title 118:17 toaster 154:18 today 6:13 9:8 14:15 16:6 20:12 43:20 44:13 68:12 92:17 178:4 today's 12:12 27:1 tolerance 149:1 toll-free 116:1,11,12 tomorrow 17:1 41:18 47:15 145:21 156:21 164:11 tonofovir 38:19 tool 165:17 topic 4:17,19 5:18 9:8 16:11 17:1 20:13 43:12,15,17 66:4</p>	<p>87:9 108:18,20 130:12,16 150:22 183:3 topics 28:3 104:2 140:11 153:10 157:3 Topyramate 147:20 total 38:9 59:12 totally 122:3 140:11 touch 101:13 163:12 tough 164:2 toward 111:12 towards 7:22 toxicological 45:8 Toxicology 178:18 trade-off 161:3 trade-offs 107:7 traditional 50:12 training 20:10 22:14 23:10 Tran 91:20 transcribed 8:14 TRANSCRIBER 192:1 transcript 192:3 transcription 189:3 transcriptionist 131:15 Transcripts 7:15 translate 142:7 translated 129:12 translation 129:10</p>
---	---	---	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 44

<p>transmission 109:17,20</p> <p>Transplant 37:8</p> <p>treat 96:12,20 151:12 183:17</p> <p>treated 94:9,10 139:2 186:5</p> <p>treatment 95:10 96:15 97:2 105:18 151:14 178:21</p> <p>treatments 96:17</p> <p>trends 46:9,10</p> <p>Treximet 96:13</p> <p>trial 11:16 68:5,10 127:11</p> <p>trials 27:17 45:15,20</p> <p>tricky 177:18</p> <p>tried 173:14</p> <p>trigger 11:19,22</p> <p>trimester 52:21 53:1 54:2 56:16 98:12,14,15 99:2,6,14 100:8 161:18,20</p> <p>trimesters 99:6</p> <p>Trinka 2:8 21:16 141:9 174:12</p> <p>tripled 145:14</p> <p>true 46:5 81:4 139:11 156:8 191:8</p> <p>truly 133:20 139:7 172:16</p> <p>truncation 51:9 58:7</p> <p>Truvada 36:21</p>	<p>38:19</p> <p>try 7:10 13:2 18:22 19:17 44:4 54:4 59:7 66:19 78:19 112:6 137:20 146:3,17 168:11 170:20 182:15</p> <p>trying 14:10 77:18 112:13 124:19 126:9,15 135:19 136:7 137:18 138:5 140:21 145:1 148:13 163:22 165:18</p> <p>turn 8:10,12 20:4 31:11 36:1 76:17</p> <p>turned 85:11</p> <p>turnover 86:13</p> <p>Twenty-five 97:15</p> <p>twice 78:11 84:6 87:11</p> <p>twofold 56:18,22 57:13 160:18</p> <p>Tylenol 143:13</p> <p>type 29:18 74:2 75:13 96:2,5,21 118:13</p> <p>types 74:8</p> <p>typewriting 191:7</p> <p>typical 50:21 178:14 180:20</p> <p>typically 45:15 46:1,10 48:22 51:18 62:8 149:21</p> <p>typo 70:13</p> <p style="text-align: center;">U</p> <p>U.K 47:13</p>	<p>U.S 95:19 98:4 172:22</p> <p>U.S.-based 36:14</p> <p>ultimately 83:6 86:4 148:4,19</p> <p>ultra 146:9</p> <p>ultrasound 75:22 76:5,21 77:13 133:11,15,21 166:15</p> <p>ultrasound-only 77:9</p> <p>unable 41:9</p> <p>unacceptable 106:10</p> <p>unanswered 89:4</p> <p>unbranded 94:22</p> <p>uncertainty 67:3 78:7 106:6</p> <p>uncommon 62:13 179:6</p> <p>unconditional 56:12 57:6</p> <p>under-ascertainment 63:17</p> <p>understand 10:4,18 15:6 126:15 129:14 151:15 153:12 186:11</p> <p>understanding 14:19 31:5 88:9 102:10 106:15 176:11 186:20</p> <p>understated 164:10</p> <p>understood 66:11</p>	<p>underway 72:1</p> <p>unenroll 138:3</p> <p>unexpected 56:1</p> <p>unexposed 51:14 54:3,7,14 55:16 59:12 76:13 77:16 78:15 82:20 83:15 121:14</p> <p>unfortunately 19:12 70:12 134:15</p> <p>uniform 143:17</p> <p>unintentional 10:6,10</p> <p>unique 95:7,19 104:6 137:4</p> <p>United 35:22 68:20 95:16 111:15,20 126:12 127:2,12 132:9</p> <p>universal 155:11</p> <p>University 21:7 22:7 25:1</p> <p>unknown 153:4 162:16</p> <p>unknowns 162:16</p> <p>Unless 55:21</p> <p>unnecessarily 66:13</p> <p>unplanned 10:9</p> <p>unrealistic 145:3</p> <p>untreated 94:9</p> <p>unvalidated 142:15</p> <p>unwilling 134:11</p>
---	---	---	--

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 45

<p>update 27:5 119:2 updated 106:8 upon 178:19 182:20 upper 144:15 usable 145:9 usage 30:10 useful 10:4 30:2 45:8 112:3 145:2,4,21 users 24:11 usually 27:16,21 30:3 45:10 72:16 88:1 114:5,13,22 115:12 116:6 117:10,21 118:22 119:10,11,14 120:18 121:12 134:16 135:3 171:5 utility 106:18 168:18 utilization 101:11 106:1 141:20</p> <hr/> <p style="text-align: center;">V</p> <hr/> <p>VA 141:11 vaccine 25:16,17 38:18,21 48:17 95:18 108:16 109:3,6,9 110:4,8 111:2,4,14,19 112:1,8 113:6,14,22 114:8,17,20 116:13,19 118:7 120:6,15 122:17,20</p>	<p>123:3,7 130:5 137:5,10 138:22 161:17 vaccines 5:13 10:1 11:21 36:7 37:5,7 39:1 91:1,7 108:10,13 109:14,18,19,22 113:5 115:14 116:9 valid 11:7 48:10 136:10 validated 49:20 validity 45:1 101:18 170:16 186:6 valproate 81:14 85:11 valproic 55:13 165:1 valuable 100:16 159:8 value 91:4 164:11 165:3 VAMPSS 22:10 25:2 variable 179:13 variables 68:10 variation 45:12 76:4 variations 132:11 varicella 37:6 38:22 109:19 varies 147:7 variety 14:11 32:7,15 189:5 various 103:14 128:21</p>	<p>Varivax 37:4 38:21 varying 94:21 153:9 VEACH 192:2,11 verbal 69:4 version 35:4 versions 95:1,14 versus 56:22 62:11 65:4 70:22 83:9 84:17,18 93:17 103:20 105:22 107:8 147:18 152:8 161:4 176:2 via 3:13 6:14 117:18 131:16 Vicki 3:8 4:3 6:3 23:6 26:21 131:12 view 65:11 102:2 127:18 150:2 186:3,7,16 views 14:16 vigorously 83:14 villus 50:14 Viread 38:19 virtually 184:6 Virus 37:6 Virus-Containing 39:1 vital 105:15 vitamin 50:5 vitamins 143:13 voice 144:4 Volume 1:11 voluntary 10:21</p>	<p>113:16 volunteer 54:18 volunteers 63:2 VSDs 79:22 166:14</p> <hr/> <p style="text-align: center;">W</p> <hr/> <p>wait 37:12 60:22 87:4 159:15 163:1 181:16 waiting 82:4 walk 112:6 Walking 121:15 warm 143:22 warrant 99:12 123:5 wary 177:10 wasn't 57:21 154:6 ways 15:22 17:16,17,18 34:15 90:17 114:2 116:18 123:3 124:3 125:9,20 141:3 wear 148:22 web 65:3 115:1 web-based 125:11,18 129:16 webcast 6:14 131:16 webpage 7:14 22:18 40:11 website 32:4,9,17 33:22 34:4 49:5 52:1 115:11,22 116:12 websites</p>
--	--	---	---

Capital Reporting Company
 Food and Drug Administration Public Meeting 05-28-2014

<p>115:6,7,11 Wednesday 1:12 week 83:3 weeks 52:13 56:1 75:5 133:5,15,21 weight 150:3 welcome 4:2 6:2,9 8:19 we'll 17:2 19:14 26:9 27:4,6 100:17 104:2 well-documented 174:4 we're 14:10,15 15:18 17:22 64:3 67:19 68:12 78:9,10 111:12 113:12 122:15 125:7,10,21 126:7 127:5,21 130:1,8 135:4 138:11 144:5 145:22 146:7,9,15 154:10 160:11 164:12 187:20 190:6 Westgate 77:2 we've 136:18 176:18 whatever 85:3 88:8,9 138:2 152:19 161:11 167:19 whatnot 68:6 135:13 Whereupon 190:9 wherever 90:15 whether 32:20</p>	<p>34:15,18,20 35:19 42:11 48:8 58:5 82:19 85:17 88:21 104:15 117:19 126:11 131:22 140:2 141:13 144:5 164:22 165:14 183:7 186:21 White 1:15 25:5 whole 14:7 15:1 45:16 184:19 188:16 whom 191:2 whose 85:9 187:7 191:4 wide 14:11,15 32:7 57:13 61:17 80:16 widely 153:9 184:18 willing 87:10 Wilson 189:9 window 161:21 witness 191:4,6,9 woman 53:13 68:18,22 69:20 70:21,22 82:3 83:1,2 84:9 132:22 133:14 136:15 178:10 woman's 135:17 women 10:2,22 27:4,16,21 28:3,14,16 29:6,19 32:2 41:19,20 42:16 45:15,21 46:2,21 48:3,13,14,20,21 49:15,19</p>	<p>50:10,22 51:10,12,17,20 52:2,8,9,13,22 53:8,10,15 54:6,15,16,22 55:7 56:15 57:2 58:5,8 60:17 63:2 65:2,12 66:7 68:19 69:16,17 70:15 76:2,3 79:9 80:6,7,10,12 81:18 83:8,9 84:16 87:7 89:16 90:7 93:3,7 95:5,20 110:1 113:16 116:8 121:5 135:21 137:13,18 138:5 139:7 142:22 143:3,19 144:15 145:13 147:11 150:12 151:7,13,15 152:5 153:22 154:16 155:7,12 159:3 170:4,10 172:22 173:1 181:3,4,8 187:17 Women's 22:13,17 32:4,17 40:11 71:4 77:3 wonder 131:22 152:13 wondered 89:22 125:2 wonderful 160:6 wondering 66:3 153:13 work 19:15 20:8,15 22:9 24:5 49:8 67:16 83:12 87:14</p>	<p>102:19 104:14 140:21 141:10 155:10,13,14 160:22 171:12 worked 20:17 86:13 87:19 91:4,7 148:4 153:9 working 17:13 31:16 135:6 168:18 180:7 workshop 8:20 13:20 world 16:14 128:21 168:1 worried 135:22 136:3 137:20 152:6 160:9 worry 50:21 135:12 145:12 152:12 178:14 180:11 worse 180:9 Wrap-up 5:19 188:3 wrestle 74:20 75:19 writing 88:16 105:9 written 135:20 wrote 168:4 <hr/> <p style="text-align: center;">Y</p> Yao 3:10 4:10 19:4,9,11 25:3,18 26:2 124:10 146:5 yearly 89:22 yet 75:9</p>
---	---	--	---

Capital Reporting Company
Food and Drug Administration Public Meeting 05-28-2014

Page 47

<p>yourself 25:20 yourselves 26:7 you've 91:10 136:8 159:5 166:22 167:4 178:10</p> <p><u>Z</u> Zostavax 37:5 38:21 Zoster 37:6 39:1</p>			
--	--	--	--
