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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
AND THE PEDIATRIC ADVISORY COMMITTEE

Tuesday, May 17, 2011
8:00 a.m. to 5:30 p.m.

Hilton Washington, DC/Silver Spring
The Ballrooms
8727 Colesville Road
Silver Spring, Maryland

1 **Winifred A. Landis, R.Ph. C.D.E.**

2 Pharmacist, CVS Pharmacy

3 Lafayette, IN

4

5 **Norma Martinez Rogers, Ph.D., R.N., FAAN**

6 *(Consumer Representative)*

7 University of Texas Health Science Center at

8 San Antonio, Department of Family Nursing

9 San Antonio, TX

10

11 **Leslie R. Walker-Harding, M.D.**

12 Chief, Division of Adolescent Medicine

13 Professor of Pediatrics

14 Seattle Children's Hospital

15 University of Washington

16 Seattle, WA

17

18 **Dorraine D. Watts, Ph.D., R.N.**

19 Professor, College of Nursing

20 St. Petersburg College

21 St. Petersburg, FL

22

1 NONPRESCRIPTION DRUGS ADVSIORY COMMITTEE (NDAC)

2 (Non-Voting)

3 Edward B. Nelson, M.D., FACP

4 (*Industry Representative*)

5 Medical Director

6 Martek Biosciences Corp. Subsidiary of Royal DSM NV

7 Austin, TX

8
9 PEDIATRIC ADVISORY COMMITTEE (PAC) MEMBERS (Voting)

10 Daniel A. Notterman, M.A., M.D.

11 Associate Dean for Research and Graduate Studies

12 Penn State College of Medicine

13 Associate Vice President for Health Sciences

14 Research

15 Penn State University

16 Professor, Pediatrics, Biochemistry and Molecular

17 Biology, Penn State Milton S. Hershey Medical

18 Center

19 Hershey, PA

20

21

22

1 **Geoffrey L. Rosenthal, M.D., Ph.D.**

2 Professor of Pediatrics, University of Maryland
3 School of Medicine
4 Director, Pediatric and Congenital Heart Program
5 Executive Director, Critical Care Services
6 University of Maryland Hospital for Children
7 Baltimore, MD

8
9 **Alexander T. Rakowsky, M.D.**

10 Institutional Review Board (IRB) Chair
11 Research Institute at Nationwide Childrens Hospital
12 Assistant Professor of Pediatrics
13 Division of Ambulatory Pediatrics
14 Nationwide Childrens Hospital
15 Columbus, OH

16
17 **Kenneth E. Towbin, M.D.**

18 Chief, Clinical Child and Adolescent Psychiatry
19 Emotion and Development Branch
20 National Institute of Mental Health (NIMH)
21 National Institutes of Health (NIH)
22 Rockville, MD

1 **Victor Santana, M.D.**

2 Member, Department of Oncology

3 St. Jude Children's Research Hospital

4 Memphis, TN

5

6 **Joseph L. Wright, M.D., M.P.H.**

7 Senior Vice President

8 Children's National Medical Center

9 The Child Health Advocacy Institute

10 Washington, DC

11

12 **PEDIATRIC ADVISORY COMMITTEE (PAC) (Non-Voting)**

13 **Henry Farrar, M.D.**

14 ***(Pediatric Health Organization Representative)***

15 Fellow, American Academy of Pediatrics

16 Department of Pediatrics

17 Arkansas Children's Hospital

18 Little Rock, AR

19

20

21

22

1 **Brahm Goldstein, M.D., M.C.R.**

2 ***(Industry Representative)***

3 Senior Medical Director, Translational Medicine

4 Ikaria, Inc.

5 Clinton, NJ

6
7 **TEMPORARY MEMBERS (Voting)**

8 **Amy J. Celento**

9 ***(Patient Representative)***

10 Nutley, NJ

11
12 **Susan S. Baker, M.D., Ph.D.**

13 Professor of Pediatrics

14 Co-Director Digestive Diseases and Nutrition Center

15 Women and Children's Hospital

16 Buffalo, NY

17
18 **Michael R. Cohen, R.Ph., M.S., Sc.D.**

19 President

20 Institute for Safe Medication Practices (ISMP)

21 Horsham, PA

22

1 **Richard Neill, M.D.**

2 ***(Acting Chair)***

3 Vice Chair, Department of Family Medicine and

4 Community Health

5 University of Pennsylvania

6 Philadelphia, PA

7
8 **Ruth M. Parker, M.D.**

9 Professor of Medicine and Public Health

10 Emory University School of Medicine

11 Atlanta, GA

12
13 **Marcus M. Reidenberg, M.D., FACP**

14 Professor of Pharmacology, Medicine and Public

15 Health

16 Weill Cornell Medical College

17 New York, NY

18

19

20

21

22

1 **TEMPORARY MEMBERS (Voting)**

2 **Marie R. Griffin, M.D., M.P.H.**

3 Professor, Department of Preventive Medicine
4 Vanderbilt University Medical Center
5 Nashville, TN

6

7 **Gary A. Walco, Ph.D., ABPP**

8 Professor of Anesthesiology
9 University of Washington School of Medicine
10 Director of Pain Medicine
11 Department of Anesthesiology and Pain Medicine
12 Seattle Children's Hospital
13 Seattle, WA

14

15 **SPEAKER (Non-Voting, Presenting Only)**

16 **Maria Suarez-Almazor, M.D., Ph.D.**

17 Barnts Family Distinguished Professor
18 University of Texas MD Anderson Cancer Center
19 Houston, TX

20

21

22

1 **FDA PARTICIPANTS (Non-Voting)**

2 **M. Scott Furness, Ph.D.**

3 Director

4 Division of Nonprescription Regulation Development

5 (DNRD), Office of Drug Evaluation IV (ODE-IV)

6 OND, CDER, FDA

7

8 **Sharon Hertz, M.D.**

9 Deputy Director

10 Division of Anesthesia and Analgesia Products

11 (DAAP), Office of Drug Evaluation II (ODE-II)

12 OND, CDER, FDA

13

14 **RADM Sandra Kweder, M.D.**

15 Deputy Director, Office of New Drugs (OND)

16 CDER, FDA

17

18 **Dianne Murphy, M.D.**

19 Director, Office of Pediatric Therapeutics (OPT)

20 Office of Commissioner (OC), FDA

21

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1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Opening Remarks	
4	Richard Neill, M.D.	15
5	Introduction of Committee	16
6	Conflict of Interest Statement	
7	Diem-Kieu Ngo, Pharm.D., BCPS	22
8	FDA Introductory Remarks	
9	M. Scott Furness, Ph.D.	28
10	FDA Presentation	
11	Regulatory History of Pediatric	
12	Acetaminophen Dosing	
13	Kathleen Phelan, R.Ph.	33
14	Clinical Pharmacology Findings of	
15	Acetaminophen in Pediatric Patients	
16	Ping Ji, Ph.D.	50
17	Literature Review: Efficacy and Safety of	
18	Acetaminophen in Children 6 Months to	
19	2 Years of Age	
20	Jane Filie, M.D.	62
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Review of Extrapolation: What It Is and	
4	Why We Use It	
5	Lisa Mathis, M.D.	77
6	Clarifying Questions	81
7	FDA PRESENTATION (continued)	
8	Introduction to Office of Surveillance and	
9	Epidemiology Presentations	
10	Irene Chan, Pharm.D., BCPS	110
11	Single-Ingredient Acetaminophen	
12	Utilization Patterns	
13	Tracy Pham, Pharm.D.	111
14	Acetaminophen-Exposure Associated Problems in	
15	Children in the U.S.: A Review of U.S. Poison	
16	Control Center Calls Data for 2002-2008	
17	Margie Goulding, Ph.D.	119
18	Clarifying Questions	137
19		
20		
21		
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	FDA PRESENTATION (continued)	
4	Hospitalization Rates for	
5	Acetaminophen-Associated Poisonings in Children	
6	Syed Rizwanuddin Ahmad, M.D., M.P.H.	161
7	Acetaminophen Overdose Among Children	
8	Maria Suarez-Almazor, M.D., Ph.D.	167
9	Clarifying Questions	175
10	FDA PRESENTATION (Continued)	
11	Review of Acetaminophen Postmarketing Adverse	
12	Event Reports and Medical Literature	
13	Peter Waldron, M.D.	190
14	Medication Errors Associated with Pediatric	
15	Use of Oral Acetaminophen	
16	Irene Chan, Pharm.D., BCPS	201
17	Clarifying Questions	223
18	INDUSTRY PRESENTATION	
19	Introductory Remarks	
20	Barbara Kochanowski, Ph.D.	245
21	Acetaminophen Pharmacokinetic Data in Children	
22	Cathy Gelotte, Ph.D.	255

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Acetaminophen Efficacy and Safety, and	
4	Weight-Based Dosing	
5	Ed Kuffner, M.D.	266
6	Safe Use of OTC Acetaminophen in Children	
7	Randall Bond, M.D.	293
8	Industry Initiatives, Concluding Remarks	
9	Barbara Kochanowski, Ph.D.	302
10	Clarifying Questions	308
11	Open Public Hearing	337
12	Clarifying Questions (continued)	368
13	Adjournment	411
14		
15		
16		
17		
18		
19		
20		
21		
22		

P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Opening Remarks

DR. NEILL: Good morning. I have 8:00, and so I'd like to go ahead and get started.

My name is Richard Neill, and I am an acting chair for the Nonprescription Drugs Advisory Committee. And just while people are gathering in your seats, I'd like to remind you all to please silence your cell phones and your Blackberrys and all other noisemaking devices that may be proximate to you.

I also want to identify the FDA press contact, Mr. Jeffrey Ventura. If you're present, can you please stand up? Jeff just came in the door, all the way in the back.

So I think most of us are seated. This is a joint meeting between the Nonprescription Drugs and Pediatric Advisory Committees. And I've already been reintroduced to several of my colleagues on NDAC. My memory being what it is, those reintroductions were necessary.

1 For the rest of you, what I'd like to do is
2 starting perhaps with the left, go around the
3 table, say who you are and what your role is here
4 in the meeting today.

5 **Introduction of the Committee**

6 DR. MURPHY: I'm Dianne Murphy. I'm a
7 pediatric infectious disease specialist and
8 Director of the Office of Pediatric Therapeutics in
9 the Office of the Commissioner. And our
10 congressional mandate is to oversee safety and
11 product development for children at the FDA.

12 DR. KWEDER: I'm Sandra Kweder. I'm an
13 internist and obstetric medicine specialist, and my
14 job is I'm the Deputy Director of the Office of New
15 Drugs.

16 DR. FURNESS: Hi. I'm Scott Furness, and I
17 am the Division Director of the Division of
18 Nonprescription Regulation Development in FDA.

19 DR. WALCO: Gary Walco, director of Pain
20 Medicine, Seattle Children's; Professor of
21 Anesthesiology, University of Washington.

22 DR. CURRY: Steven Curry, Director,

1 Department of Medical Toxicology, Banner Good
2 Samaritan Hospital in Phoenix, and with the
3 University of Arizona College of Medicine in
4 Phoenix.

5 DR. PARKER: Ruth Parker, Professor of
6 Medicine and Public Health, Emory University. I'm
7 an SGE here visiting you today.

8 DR. WALKER-HARDING: Leslie Walker-Harding,
9 Professor of Pediatrics, Chief of the Division of
10 Adolescent Medicine at University of Washington and
11 Seattle Children's.

12 DR. FARBER: Neil Farber. I'm Director of
13 the Internal Medicine Group, La Jolla, and
14 Professor of Medicine, UC-San Diego.

15 DR. GRIFFIN: Marie Griffin, Professor of
16 Preventive Medicine and Medicine at Vanderbilt
17 University.

18 DR. ROGERS: I'm Norma Martinez Rogers, and
19 I'm a professor at UT Health Science Center School
20 of Nursing, San Antonio, and I am a consumer
21 representative for PAC.

22 DR. LANDIS: Good morning. Wini Landis,

1 community pharmacist from Lafayette, Indiana, with
2 CDS.

3 DR. ENGLE: Good morning. I'm a pharmacist.
4 Jan Engle. I'm the Executive Associate Dean and
5 Professor and Head of the Department of Pharmacy
6 Practice at University of Illinois at Chicago,
7 College of Pharmacy.

8 DR. ROSENTHAL: Good morning. My name is
9 Geoff Rosenthal. I'm a pediatric cardiologist and
10 Professor of Pediatrics at the University of
11 Maryland School of Medicine, and I chair the
12 Pediatric Advisory Committee.

13 DR. NEILL: And I'm Richard Neill. I'm a
14 family physician, Vice Chair and Assistant
15 Professor at the University of Pennsylvania,
16 Department of Family Medicine and Community Health.

17 CDR NGO: Commander Diem-Kieu Ngo. I'm the
18 Designated Federal Officer for this meeting.

19 MS. CELENTO: Amy Celento, the patient-
20 family representative.

21 DR. WATTS: Dorraine Watts, Professor of
22 Nursing at St. Petersburg College, in biostatistics

1 and research design.

2 DR. REIDENBERG: I'm Marcus Reidenberg. I'm
3 another professor, this time in Pharmacology,
4 Medicine and Public Health at Weill Cornell Medical
5 College, and I run the clinical pharmacology
6 program.

7 DR. COHEN: I'm Mike Cohen. I'm with the
8 Institute for Safe Medication Practices, and I'm a
9 pharmacist.

10 DR. BAKER: I'm Susan Baker. I'm Professor
11 of Pediatrics at the University of Buffalo and
12 Division Director for Pediatric Gastroenterology.

13 DR. NOTTERMAN: I'm Daniel Notterman. I'm
14 Professor of Pediatrics and Molecular Biology and
15 Vice Dean at Penn State College of Medicine. I'm a
16 member of the Pediatric Advisory Committee.

17 DR. SANTANA: Good morning. I'm Victor
18 Santana. I'm a pediatric hematologist-oncologist
19 in the Department of Oncology at St. Jude
20 Children's Research Hospital, and my clinical
21 research interests are in new drug development of
22 anticancer drugs in children, and I'm also a member

1 of the Pediatric Advisory Committee.

2 DR. RAKOWSKY: Good morning. My name is
3 Alex Rakowsky. I'm also a member of the Pediatric
4 Advisory Committee. I'm the IRB chair at
5 Nationwide Children's Hospital in Columbus, Ohio.

6 DR. FARRAR: I'm Henry Farrar. I'm a
7 pediatric clinical pharmacologist and emergency
8 medicine specialist and professor of pediatrics at
9 Arkansas Children's Hospital. And I am on the
10 Pediatric Advisory Committee as a nonvoting member,
11 representing pediatric health care organizations.

12 DR. GOLDSTEIN: Good morning. I'm Brahm
13 Goldstein. I'm a pediatric critical care
14 physician. I'm Clinical Professor of Pediatrics at
15 University of Medicine and Dentistry-New Jersey.
16 I'm Senior Medical Director at Ikaria in Clinton,
17 New Jersey, and I am the industry representative to
18 the Pediatric Advisory Committee.

19 DR. NELSON: Good morning. Last, but I hope
20 not least, Ed Nelson. I'm the industry
21 representative on the Nonprescription Drug
22 Committee. I am a medical director at Martek

1 Biosciences and retired academic and industry
2 representative from other companies.

3 DR. NEILL: Thanks very much. We do have
4 one or two members that I believe may be coming in
5 later due to traffic and travel concerns.

6 For those of you that haven't been to a
7 meeting before, now is the time where I get to read
8 the standard disclosure.

9 For topics such as those discussed at
10 today's meeting, there are often a variety of
11 opinions, some of which are strongly held. Our
12 goal is that today's meeting will be a fair and
13 open forum for discussion of these issues and that
14 individuals can express their views without
15 interruption. Thus, as a gentle reminder,
16 individuals will be allowed to speak into the
17 record only if recognized by the chair. We look
18 forward to a productive meeting.

19 In the spirit of the Federal Advisory
20 Committee Act and the Government in the Sunshine
21 Act, we ask that the advisory committee members
22 take care that their conversations about the topic

1 at hand take place in the open forum of the
2 meeting.

3 We are aware that members of the media are
4 anxious to speak with the FDA about these
5 proceedings. However, FDA will refrain from
6 discussing the details of this meeting with the
7 media until its conclusion. Also, the committee is
8 reminded to please refrain from discussing the
9 meeting topic during breaks or lunch. Thank you.

10 Commander?

11 **Conflict of Interest Statement**

12 CDR NGO: I'd like to now read the conflict
13 of interest statement for the meeting. The Food
14 and Drug Administration is convening today's
15 meeting of the Nonprescription Drugs and Pediatric
16 Advisory Committees under the authority of the
17 Federal Advisory Committee Act of 1972.

18 With the exception of the industry
19 representatives, all members and temporary voting
20 members of the committees are special government
21 employees or regular federal employees from other
22 agencies and are subject to federal conflict of

1 interest laws and regulations.

2 The following information on the status of
3 these committees' compliance with federal ethics
4 and conflict of interest laws, covered by, but not
5 limited to, those found at 18 USC Section 208 and
6 Section 712 of the Federal Food, Drug, and Cosmetic
7 Act, is being provided to participants in today's
8 meeting and to the public.

9 FDA has determined that members and
10 temporary voting members of these committees are in
11 compliance with federal ethics and conflict of
12 interest laws. Under 18 USC Section 208, Congress
13 has authorized FDA to grant waivers to special
14 government employees and regular federal employees
15 who have potential financial conflicts when it is
16 determined that the agency's need for a particular
17 individual's services outweighs his or her
18 potential financial conflict of interest.

19 Under Section 712 of the FD&C Act, Congress
20 has authorized FDA to grant waivers to special
21 government employees and regular federal employees
22 with potential financial conflicts when necessary

1 to afford the committee essential expertise.

2 Related to the discussions of today's
3 meeting, members and temporary voting members of
4 these committees have been screened for potential
5 financial conflicts of interests of their own, as
6 well as those imputed to them, including those of
7 their spouses or minor children, and, for purposes
8 of 18 USC Section 208, their employers.

9 These interests may include investments,
10 consulting, expert witness testimony, contracts,
11 grants, CRADAs, teaching, speaking, writing,
12 patents and royalties, and primary employment.

13 Today's agenda involves a review of
14 pertinent pharmacokinetic safety and efficacy data
15 and discussion of whether new dosing information
16 for oral over-the-counter drug products containing
17 acetaminophen should be added to the label for
18 children less than 2 years of age. In addition,
19 the committees will consider adding to the label a
20 weight-based dosing regimen to the existing age-
21 based dosing regimen for children 2 to 12 years of
22 age, which is currently in the label. Dosing for

1 children 12 years of age and older will not be
2 discussed.

3 Lastly, the committees will discuss ways the
4 administration of these products by caregivers can
5 be improved so that medication errors can be
6 minimized. This is a particular matters meeting
7 during which general issues will be discussed.

8 Based on the agenda for today's meeting and
9 all financial interests reported by the committee
10 members and temporary voting members, no conflict
11 of interest waivers have been issued in conjunction
12 with this meeting.

13 To ensure transparency, we encourage all
14 standing committee members and temporary voting
15 members to disclose any public statements that they
16 may have made concerning the issues before the
17 committees.

18 With respect to FDA's invited industry
19 representative, we would like disclose that
20 Drs. Brahm Goldstein and Edward Nelson are
21 participating in this meeting as nonvoting industry
22 representatives acting on behalf of regulated

1 industry. Drs. Goldstein's and Nelson's roles at
2 this meeting are to represent industry in general
3 and not any particular company.

4 Dr. Goldstein is currently employed by
5 Ikaria. Dr. Nelson, a former employee of Johnson &
6 Johnson, receives a pension from Johnson & Johnson
7 and owns stock in J&J. Dr. Nelson is currently
8 employed by Martek Biosciences Corporation.

9 Lastly, we would like to disclose that
10 Dr. Marie Suarez-Almazor is participating in
11 today's meeting as a guest speaker. Dr. Suarez-
12 Almazor will not participate in the committees'
13 deliberations nor will she vote.

14 We would like to remind members and
15 temporary voting members that if the discussions
16 involve any other products or firms not already on
17 the agenda for which an FDA participant has a
18 personal or imputed financial interest, the
19 participants need to exclude themselves from such
20 involvement and their exclusion will be noted for
21 the record. FDA encourages all other participants
22 to advise the committees of any financial

1 relationships that they may have with any firms at
2 issue.

3 Thank you.

4 DR. NEILL: In my nine years as a residency
5 program director doing interviews for residents
6 coming from around the country, one rule held fast,
7 and that was that the applicants who lived closest
8 were always the latest. And in that spirit, we've
9 got two more members and another staff that have
10 joined us, and I wonder if you could introduce
11 yourself.

12 DR. WRIGHT: Joseph Wright. I'm Senior Vice
13 President at Children's National Medical Center
14 here in Washington and Professor of Emergency
15 Medicine and Health Policy.

16 DR. TOWBIN: And I'm Kenneth Towbin. I'm a
17 child and adolescent psychiatrist at the intramural
18 program at the National Institute of Mental Health.

19 DR. HERTZ: Good morning. I'm Sharon Hertz,
20 Deputy Director of the Division of Anesthesia,
21 Analgesia, and Addiction Products at FDA.

22 DR. NEILL: Welcome to you all. We do know

1 that you didn't think it was going to take as long
2 as it did.

3 So we have a busy agenda today, and I think
4 we're going to start with Dr. Furness, who is going
5 to brief us on the background of the topic for the
6 meeting today and tomorrow.

7 DR. FURNESS: Good morning. I would like to
8 welcome everyone to the joint Nonprescription and
9 Pediatric Advisory Committee meeting to discuss the
10 use of OTC acetaminophen products in children. I'd
11 like to especially thank the committees for your
12 efforts and look forward to the discussion and
13 recommendations.

14 My name is Scott Furness and I'm the
15 Division Director of the Division of
16 Nonprescription Regulation Development, and I will
17 be offering some introductory remarks.

18 So to begin, I would like to briefly comment
19 on the scope of today's meeting. As you can see on
20 this slide, there are a number of pediatric OTC
21 products containing acetaminophen, but the main
22 point I want to draw your attention to is that the

1 products being discussed today and tomorrow are
2 those products on the right-hand side of the slide.
3 So these are the products that will be discussed
4 today and tomorrow at the advisory committee
5 meetings.

6 Acetaminophen suppository products, shown
7 here on the left, are currently being marketed
8 under OTC new drug applications, and they will not
9 be discussed at the meeting. You will hear more
10 about the OTC monograph system and how it differs
11 from the new drug application process in the next
12 presentation.

13 So to begin, we are convened to address this
14 rather simple-appearing question; namely, are the
15 existing dosing directions and age breakdowns
16 sufficient to appropriately administer OTC
17 acetaminophen-containing drug products to children.

18 In 1999, the agency received a citizen
19 petition regarding just this very question, and the
20 citizen petition makes the following points;
21 namely, that physicians very frequently recommend
22 to consumers the use of pediatric acetaminophen in

1 children less than 2 years of age; and on their
2 own, the firm developed dosing schedules that were
3 designed to very closely correlate with the
4 administration of acetaminophen in the dose of 10
5 to 15 milligrams per kilogram of body weight per
6 single dose. And these recommendations were made
7 available in a number of different professional
8 materials, such as the Physician's Desk Reference.

9 So based on those conclusions, the
10 petitioners asked the agency to take the following
11 actions; namely, to expand the age groups for OTC
12 consumer dosing instructions to include children
13 2 months old to less than 2 years of age, as well
14 as to include age and weight-based dosing for
15 children less than 12 years of age.

16 Now, although it should be noted that in
17 later communications, the firm later revised their
18 request for that lower age bound from 2 months to
19 6 months. And to put these requests in context,
20 please also note that the current dosing in the
21 agency's proposed regulation allows the following
22 dosing directions; namely, for kids less than

1 2 years of age, there are no dosing instructions
2 provided on the label, and it only states "consult
3 with a physician," whereas, for children ages 2 to
4 12, there's currently only age-based dosing that's
5 allowed under FDA's proposed regulation.

6 In terms of the agenda of the meeting, we'd
7 like to start off with a number of presentations,
8 including presentations by the FDA and FDA's
9 invited speaker, and it will cover a whole hosts of
10 different topics, such as the regulatory history,
11 the pharmacokinetics, the medication errors,
12 safety, efficacy extrapolation, drug utilization
13 patterns, as well as a whole host of epidemiology
14 presentations.

15 Just after lunch this afternoon, we will
16 hear from industry, and that will be followed by
17 the open public hearing, and then the discussion
18 and voting phases of the meeting. And those are
19 certainly the most important parts of the meeting,
20 and they are why we have brought you here today and
21 tomorrow.

22 The questions for the advisory committee

1 include a mix of discussion and voting questions.
2 And speaking of the discussion questions, here they
3 are.

4 I would remind you that with these we will
5 ask you to discuss, and, where appropriate, provide
6 recommendations for the agency's consideration.

7 Question number 1, should weight-based
8 dosing be added to the existing age-based label
9 dosing directions for children ages 2 to 12. And
10 if the answer to that question is yes, how should
11 the dosing directions be written using incremental
12 increases in dosing based on age and weight?

13 Question number 2, do the pharmacokinetic,
14 safety and efficacy data support the addition of
15 new label dosing directions corresponding to a 10
16 to 15 milligram per kilogram dose for children ages
17 6 months to 2 years of age. And if the answer to
18 that question is yes, should the new labeling
19 include both antipyretic and analgesic claims?

20 Question number 3 is a discussion question;
21 namely, in what ways can the labeling, packaging,
22 and the container closure system be improved such

1 that the medication errors can be minimized?

2 Lastly, question number 4, restricting
3 liquid formulations to a single concentration was a
4 recommended intervention discussed at a recent 2009
5 AC that addressed specifically acetaminophen
6 safety; and, should the agency consider similar
7 measures for pediatric acetaminophen-containing
8 solid oral dosage forms?

9 So with that, I'm going to close. Again,
10 I'd like to thank the committee for your efforts
11 and very much look forward to the discussion. And
12 with that, I will end and turn the meeting back to
13 the chair.

14 DR. NEILL: Thank you, Dr. Furness.

15 Before the next presentation, I want to
16 announce to those of you that are seeking Internet
17 access, there is a wireless network by the hotel
18 only. Thank you.

19 So now I think we're going to hear from
20 Dr Phelan and Dr. Mathis.

21 **FDA Presentation - Kathleen Phelan**

22 DR. PHELAN: Good morning. I'm Kate Phelan

1 from the Division of Nonprescription Regulation
2 Development. Today I will tell you how over-the-
3 counter drugs are regulated and the regulatory
4 history of acetaminophen use in children.

5 Here is what you'll see if you go to the
6 drugstore looking for an analgesic today, a lot of
7 product choices, but only four active ingredients:
8 aspirin, acetaminophen, ibuprofen, and naproxen.
9 These products are not all regulated in the same
10 way. They receive different levels of regulatory
11 oversight, as I will explain.

12 Today I will present four main topics. One,
13 how over-the-counter drug products are regulated;
14 two, the acetaminophen products that are available
15 today without a prescription or over-the-counter;
16 three, the regulatory history of over-the-counter
17 acetaminophen with an emphasis on dosing for
18 children under 12 years of age; and, four, what
19 previous advisory committees recommended that
20 pertains to acetaminophen use in children.

21 First, how over-the-counter drug products
22 are regulated. These are some of the acetaminophen

1 products available for use in children. As
2 Dr. Furness mentioned, they are regulated under two
3 different processes, the new drug application, or
4 NDA, and the OTC drug monograph. Many more
5 children's acetaminophen products are regulated
6 under the monograph than under the NDA. In fact,
7 the only children's acetaminophen product regulated
8 under an NDA is the suppository. This is because
9 differences between the two processes make
10 marketing products under the monograph simpler than
11 marketing under an NDA.

12 Let's look at just three of the differences.
13 First, an NDA review evaluates the final drug
14 product. This means the active ingredient is
15 evaluated in the formulation that will be used by
16 the consumer, including the specific inactive
17 ingredients and manufacturing process used to
18 produce that product. The monograph process
19 evaluates only the active ingredient. The final
20 drug product in the formulation that will be used
21 by the consumer is not evaluated.

22 Second, under the NDA process, each drug

1 product must receive FDA approval before it can be
2 marketed. This requires product sponsors to
3 conduct studies and submit data to FDA.

4 Conversely, if an active ingredient is generally
5 recognized as safe and effective in a monograph,
6 drug products containing that ingredient can be
7 marketed without prior FDA approval, as long as
8 they follow the monograph.

9 Third, the contents of NDAs are
10 confidential, proprietary information, whereas the
11 monograph process is a public process and all data
12 must be available publicly. This means that data
13 submitted in an NDA cannot be transferred to the
14 monograph process unless the data are available
15 publicly through publication or posting to a
16 docket.

17 Considering that bringing a product to
18 market under the NDA process is more difficult,
19 expensive and time-consuming, why would a
20 manufacturer submit an NDA? Well, because of the
21 restrictions that apply to monograph products. A
22 monograph is analogous to a recipe. It specifies

1 allowable active ingredients, indications,
2 populations, doses, and other aspects of the
3 product. Also, timed-release products cannot be
4 marketed under a monograph. This is because the
5 formulation of a timed-release product is integral
6 to the product's effect and must be evaluated.

7 Both the NDA and the monograph are actively
8 used today to regulate over-the-counter drugs. But
9 why are there two processes? The NDA started when
10 Congress passed the Food, Drug, and Cosmetic Act in
11 1938. The Act required drug products to show
12 evidence of safety before they could be marketed.
13 In 1962, the Act was amended to require evidence of
14 effectiveness as well as safety. Additionally, the
15 1962 amendments required that all drugs brought to
16 market since 1938 be evaluated for effectiveness,
17 whether prescription or OTC.

18 A range of OTC drug products that
19 represented the general market was evaluated by the
20 National Academy of Sciences and National Research
21 Council. Of the 420 OTC products reviewed, only
22 25 percent were found to be effective for a labeled

1 indication. At the time, there were an estimated
2 100,000 to 1 million products sold over-the-
3 counter, most of which had never been reviewed.

4 The lack of efficacy found in the small
5 initial review confirmed the need to review these
6 products. But how? The solution was the OTC drug
7 review, or monograph process, which began in 1972.
8 The OTC drug review was designed to streamline the
9 task by evaluating large numbers of products
10 simultaneously.

11 How does the OTC drug monograph process do
12 this? To begin, FDA divided the OTC drug market
13 into 26 therapeutic categories under which active
14 ingredients would be reviewed. The monograph
15 process was initiated in 1972 with a Federal
16 Register notice that listed these therapeutic
17 categories and described what kinds of data were
18 needed and how they should be presented.

19 FDA issued calls for data on each
20 therapeutic category. Advisory review panels,
21 similar to today's advisory committees, reviewed
22 the submitted data. The panels recommended which

1 active ingredients should be generally recognized
2 as safe and effective, or GRAS and GRAE, and not
3 misbranded, and under what conditions.

4 For example, they recommended that
5 acetaminophen be GRAS and GRAE when used as an
6 analgesic or antipyretic at a dose of
7 325 milligrams every four hours in adults. They
8 also recommended that acetaminophen not be gray as
9 antirheumatic. The panel's reports were published
10 in the Federal Register beginning the first round
11 of public comments.

12 Here is an overview of the monograph
13 process. Advisory review panels reviewed data
14 submitted by drug companies and other interested
15 parties. The panels made recommendations on the
16 safety and effectiveness of each active ingredient
17 under specific conditions of use.

18 Each panel's report was published in the
19 Federal Register as an advance notice of proposed
20 rulemaking, or ANPR, and the public was invited to
21 comment. Using the comments and the panel reports,
22 FDA develops and publishes the tentative final

1 monograph, or TFM, usually called the proposed
2 rule. Again, the public is invited to comment.

3 Finally, FDA uses the comments and proposed
4 rule to write a final monograph, which is published
5 in the Federal Register. The regulations section
6 of the final monograph has the force of law and is
7 published in the subsequent Code of Federal
8 Regulations as the therapeutic category monograph.

9 Where is acetaminophen in this multistep
10 process? Acetaminophen is in the internal
11 analgesic, antipyretic, and antirheumatic
12 therapeutic category, which I will call IAAA. The
13 IAAA ANPR was published in 1977. The IAAA proposed
14 rule was published in 1988. The IAAA final
15 monograph has not been published yet.

16 There are a number of therapeutic categories
17 for which final monographs have not been published.
18 This is because constantly emerging issues and new
19 data bring forth questions which are often complex
20 and difficult to resolve to everyone's
21 satisfaction.

22 I just told you a little bit about the two

1 processes for regulating OTC drug products. Now,
2 we will look at available products. We'll start
3 with products approved and marketed under NDAs.
4 The IAAA proposed rule specifies oral
5 administration. Therefore, rectal suppositories
6 require an NDA. Four strengths of suppositories
7 are approved under NDAs for consumers of all ages.
8 I've highlighted those labeled for use in children
9 under 12 years old.

10 Over-the-counter NDA products usually
11 conform to monograph conditions, but because they
12 are approved individually, they may differ from
13 monograph products in significant ways. For
14 example, the 80 milligram strength suppository is
15 labeled for use in children aged 6 to 36 months.
16 Currently, the IAAA proposed rule does not include
17 labeling of OTC acetaminophen for children younger
18 than 2 years. Also marketed under NDAs are
19 acetaminophen extended-release tablets. These are
20 labeled only for consumers aged 12 years and over.

21 Now, let's see products that are marketed
22 under the monograph process. Under the monograph,

1 we have both solid and liquid, oral, immediate-
2 release dosage forms. This slide shows the solid
3 oral dosage forms. Strengths range from 80 to
4 500 milligrams per dosing unit, and they are
5 labeled for consumers 2 years and older, consistent
6 with the IAAA proposed rule.

7 Now, I had thought that there were three
8 concentrations of oral liquid acetaminophen
9 products available, but a recent visit to the
10 drugstore turned up a fourth. Three of these
11 concentrations are labeled for children aged
12 2 years and older.

13 Now, let's go back to the store. Your
14 3-year-old has become fussy and a little feverish
15 on a Sunday evening. You go to the local drugstore
16 and find these three boxes on the shelf. Looking
17 at the boxes, you see that they all contain
18 acetaminophen and one is for ages 2 to 3, one is
19 for ages 2 to 5, and one is for ages 2 to 11.

20 Now, I'm sure that everyone in this room
21 would turn the boxes around to view the drug facts.
22 This is where you see that each of these products

1 is a different concentration and the dosing
2 directions for a 3-year-old for each of these
3 products is different, ranging from 1.6 milliliters
4 for PediaCare to 5 milliliters or one teaspoon for
5 Q-PAP.

6 The dose for a 3-year-old in the IAAA
7 proposed rule is 160 milligrams, and that is the
8 labeled dose on each of these products, but the
9 quantity measured is different. This could be a
10 source of confusion, especially for a parent who
11 switches products. And we acknowledge the
12 industry's recent-announced initiative to
13 voluntarily limit children's liquid acetaminophen
14 products to one concentration.

15 I talked about some of the differences
16 between the NDA and monograph regulatory processes
17 and about the monograph process in detail. Now,
18 let's see how acetaminophen, especially dosing for
19 children under 12 years of age, traveled through
20 these regulatory processes.

21 Acetaminophen was approved under an NDA as a
22 prescription product in or before 1955. In 1955, a

1 rule was finalized that first allowed it to be sold
2 over the counter under certain conditions. One of
3 the conditions was that it would not be labeled for
4 use in children under 6 years old. This exemption
5 from prescriptions was based on citizen petitions
6 and marketing experience showing safe use.

7 In 1959, the exemption was revised to allow
8 over-the-counter sale with labeling for children
9 aged 3 years and older. In 1972, the monograph
10 process began. Oral, immediate-release
11 acetaminophen products moved from the NDA to the
12 monograph regulatory process in the IAAA category.
13 In 1977 and 1988, respectively, the IAAA ANPR and
14 proposed rule were published in the Federal
15 Register. Both included dosing for children ages
16 2 years and older, as recommended by the original
17 advisory review panel.

18 On the way from the 1977 ANPR to the 1988
19 proposed rule, FDA received some comments pertinent
20 to our discussion here. Several comments on the
21 1977 ANPR suggested that children be dosed by
22 weight. Some suggested using weight instead of

1 age. Others suggested including both weight and
2 age-based dosing on labels.

3 In the 1988 proposed rule, FDA responded
4 that age is an acceptable basis for dosing because
5 doses based on age correlate with doses based on
6 body surface area. However, FDA also responded
7 that weight-based dosing for children would be
8 discussed and considered in a future rulemaking.

9 Here is a simplified picture of the
10 currently proposed monograph dosing for
11 acetaminophen. The proposed dosing for children
12 from 2 to under 12 years old is based on body
13 surface area, although it is presented by age for
14 ease of use.

15 At the age of 6, the calculated dose is
16 325 milligrams, the same as the lowest adult dose.
17 Because acetaminophen data were lacking, this
18 dosing was based on aspirin data and studies
19 showing that aspirin and acetaminophen are safe and
20 effective in the same dosage range.

21 What has happened since publication of the
22 IAAA proposed rule in 1988? Since publication of

1 the proposed rule, there have been four advisory
2 committees that made recommendations pertinent to
3 pediatric use of acetaminophen. Let's look at
4 those now.

5 Acetaminophen use in children was not the
6 focus of all four meetings. The focuses of the
7 meetings were pediatric dosing of over-the-counter
8 products in general, pediatric dosing and labeling
9 of over-the-counter analgesic and antipyretic
10 drugs, safety issues related to unintentional
11 acetaminophen overdose, and liver injury associated
12 with the use of acetaminophen.

13 The relevant recommendations from these four
14 meetings are shown together here. These
15 recommendations will be discussed in more detail by
16 other speakers, so this is an overview.

17 Previous advisory committees have
18 recommended that FDA dose by weight, but include
19 age-based dosing because weight is not always
20 known; base pediatric dosing on data; allow only
21 one concentration of pediatric liquid acetaminophen
22 on the over-the-counter market; and include dosing

1 for infants 2 months and older on labels of over-
2 the-counter acetaminophen products, with a warning
3 that any child under 6 months of age must see a
4 doctor for fever. Because of this recommended
5 warning, FDA currently believes that over-the-
6 counter acetaminophen products should not be
7 labeled for children under 6 months old. We
8 received a citizen petition in response to some of
9 these recommendations.

10 Citizens' petitions may be submitted by the
11 public to request changes in an OTC monograph at
12 any stage of its development. After the 1997
13 advisory committee meeting, in 1999, McNeil
14 Consumer Healthcare submitted a citizen petition
15 requesting that dosing directions for children aged
16 2 months and older be allowed in acetaminophen
17 labeling under the monograph. As Dr. Furness
18 mentioned, that was later revised to 6 months and
19 older.

20 The petition included a proposed dosing
21 schedule developed at McNeil and based on dosing
22 proposed in a publication by Dr. Anthony Temple in

1 1983. McNeil's schedule includes age and weight-
2 based dosing for ages 0 to 12 years and weights 6
3 to 95 pounds. It was designed to achieve doses of
4 10 to 15 milligrams per kilogram. This schedule
5 has been available through the Physician's Desk
6 Reference since the mid 1980s.

7 Here is a chart showing McNeil's dosing
8 schedule for different age and weight groups by
9 Tylenol brand product. This version shows only
10 dosing for children under 2 years old. If you
11 can't read this, don't worry, other presenters will
12 go into the nuts-and-bolts of children's dosing.

13 I obtained this and the schedule on the
14 pervious slide from the tylenolprofesssional.com
15 website. While the schedule developed at McNeil
16 has been available in the PDR and the medical
17 literature since the early 1980s, now this schedule
18 and others are freely available online. FDA
19 recognizes the need for standardized, evidence-
20 based dosing for children and has been working
21 toward that goal.

22 As I mentioned, since publication of the

1 IAAA proposed rule in 1988, there have been four
2 advisory committee meetings that at least touched
3 on pediatric use of acetaminophen. The first of
4 those meetings, held in 1995, was partly in
5 response to public comments requesting uniform
6 pediatric dosing across therapeutic categories.
7 Some comments suggested using standard fractions of
8 the adult dose, such as one-eighth the adult dose
9 for children under 2 years, two-eighths for
10 children 2 to 3 years, and so on. However, the
11 1995 and subsequent advisory committees called for
12 data-driven, drug-specific children's dosing.

13 Historically, data to support children's
14 dosing regimens has been limited, because in the
15 past, children were generally excluded from
16 clinical trials. Given this lack of pediatric
17 data, legislation was passed to both encourage and
18 require pediatric drug development. These laws
19 include the Best Pharmaceuticals for Children Act
20 and the Pediatric Research Equity Act. However,
21 these laws apply to new drug applications and do
22 not apply to monograph active ingredients.

1 The available acetaminophen data will be
2 presented by other speakers. Thank you.

3 DR. NEILL: I think we are going to hear
4 from Dr. Mathis.

5 So in her absence, I think what we'll do is
6 accelerate the presentation and move on to Dr. Ji.

7 **FDA Presentation - Ping Ji**

8 DR. JI: Good morning. My name is Ping Ji.
9 I'm a clinical pharmacologist in the Office of
10 Clinical Pharmacology. Today I'm going to present
11 the clinical pharmacology findings of acetaminophen
12 in pediatric patients.

13 In my presentation, I'm going to cover three
14 main areas. First is the literature review of
15 acetaminophen metabolism and the effect of enzyme
16 maturation on various metabolic pathways. Then I'm
17 going to present the pharmacokinetics of
18 acetaminophen in pediatric patients and compare it
19 with adult data. At the end, I will discuss the
20 dose-response relationship for fever reduction.
21 After my presentation, you will also hear from Dr.
22 Jane Filie on additional efficacy data review in

1 pediatric patients.

2 Let me start the presentation with
3 acetaminophen metabolism and the maturation of
4 various metabolic pathways. In humans,
5 acetaminophen is metabolized in the liver primarily
6 by glucuronidation and sulfation, and like by
7 oxidation and hydroxylation. None of these
8 metabolites have any pharmacodynamic effects,
9 including pain relief and fever reduction, and none
10 of them is toxic, except this reactive intermediate
11 from the oxidation pathway.

12 This reactive intermediate is called
13 N-acetyl-p-benzo-quinone imine, or NAPQI. After it
14 is formed, it can be quickly conjugated with
15 glutathione and it further metabolizes to nontoxic
16 downstream metabolites. NAPQI may cause
17 hepatotoxicity after massive acute overdose.
18 However, at the therapeutic dose, the level of
19 circulating NAPQI is slow. It can be quickly
20 converted to nontoxic metabolites, and, therefore,
21 it is not likely to produce liver toxicity.

22 As the contribution of the hydroxylation

1 pathway is insignificant and of no clinical
2 importance, I will focus the discussion on the
3 other three metabolic pathways in this
4 presentation.

5 In adults, the glucuronidation pathway
6 contributes most to acetaminophen metabolism.
7 Fifty to 60 percent of administered dose is
8 eliminated through this pathway. The sulfation
9 pathway comes next. Twenty-five to 30 percent of
10 the dose is eliminated through the sulfation
11 pathway. In addition, less than 10 percent of the
12 dose is eliminated through the oxidation pathway,
13 and less than 5 percent of the dose is
14 hydroxylated.

15 In pediatrics, however, the contribution of
16 each metabolic pathway of age is a moving target,
17 meaning that relative contribution continues to
18 change with age in early childhood, and this is
19 largely due to the different maturation rates of
20 contributing enzymes. Sulfation pathways mature
21 very early in life, whereas glucuronidation and
22 oxidation pathways are immature in younger

1 pediatrics.

2 Next, I am going to explain the contribution
3 of each of these three pathways with age one-by-
4 one. First, let's look at the glucuronidation
5 pathway. Miller, in 1976, evaluated the metabolism
6 and elimination of acetaminophen following
7 10 milligram per kilo oral dose in neonates,
8 children and adults. A lower percentage of the
9 dose was excreted as glucuronide conjugate in
10 neonates and younger children compared to older
11 children and adults. Similar findings were also
12 seen in other people's work. The pathway being
13 immature in younger pediatrics is now well
14 recognized.

15 In contrast to the age-related excretion
16 pattern for glucuronide conjugates, a higher
17 percentage of the dose was excreted in urine as
18 sulfate conjugates in neonates and younger children
19 as compared to the older children and adults, and,
20 therefore, it appeared to compensate for the
21 smaller fraction excreted as glucuronide conjugates
22 in the young age groups.

1 In children 12 years of age, the excretion
2 pattern of acetaminophen conjugates was similar to
3 that in adults. From these data, Miller concluded
4 that younger children are more dependent on the
5 sulfate pathway in metabolizing acetaminophen than
6 older children or adults.

7 Oxidation is most limited by CYP2E1.
8 Vieira, in 1996, published their investigation on
9 the expression of CYP2E1 in human liver
10 development. Their results showed that CYP2E1
11 protein expression was absent in fetal liver, but
12 appeared right after birth, regardless of
13 gestational age. The level of CYP2E1 proteins
14 gradually increased during the first year and
15 approached adult levels between 1 to 10 years.
16 This showed that younger pediatrics have the
17 capability of generating reactive intermediate
18 NAPQI, but may form less toxic reactive
19 intermediate as compared to older pediatrics and
20 adults. This is also consistent with the result
21 that downstream oxidated metabolites were not
22 detectable in infants at 20 milligrams per kilo

1 oral dose from van der Marel's 2003 publication.

2 To summarize this section, sulfation
3 predominates acetaminophen metabolism in younger
4 pediatrics. The expression of CYP2E1 is less in
5 neonates and in young infants, and it gradually
6 reaches adult level within 1 to 10 years of age,
7 indicating that younger pediatrics may form less
8 reactive intermediate NAPQI and, therefore, may not
9 be susceptible to the reactive intermediate-
10 associated hepatotoxicity.

11 Next, I'm going to discuss acetaminophen PK
12 in pediatric patients. In this section, I'm going
13 to present PK based on a literature summary. I
14 will also compare the pediatric exposure with that
15 in adults after the currently proposed OTC
16 monograph dose.

17 To evaluate acetaminophen PK in pediatric
18 patients, we searched the public domain on
19 pediatric studies with patients less than 12 years
20 of age. Subjects were given an oral dose of
21 acetaminophen either as a single dose or multiple
22 doses. At least one of these PK measurements were

1 made, Tmax, half-life, AUC, and Cmax.

2 Based on these criteria, we identified eight
3 main publications. In addition, McNeil also
4 submitted their in-house data summary from two
5 studies conducted in pediatrics. These eight
6 published studies, along with two in-house studies,
7 form a total of more than 200 pediatric patients
8 that comprise this PK summary. This combined
9 database includes pediatrics aged between neonate
10 to 13 years. The oral dose of 5 to 30 milligrams
11 per kilo was administered.

12 The mean half-life from these studies varied
13 from 1.4 to 3.1 hours and mean Tmax varied from .5
14 to 1.8 hours. After multiple doses, no minimum
15 accumulation was observed. These results are all
16 consistent with adult data. As you can see, the
17 dose varied from 5 to 30 milligrams per kilo.

18 To further evaluate what would be the
19 exposure after oral dose administrations at the
20 proposed 10 to 15 milligrams per kilo, we
21 normalized the pediatric exposure with 10 and
22 15 milligrams per kilo and compared the Cmax and

1 AUC with adult data, as shown in the next couple of
2 slides.

3 This slide summarizes the dose normalized
4 Cmax. On the left, you see Cmax normalized to
5 10 milligrams per kilo. On the right, you see Cmax
6 normalized to 15 milligrams per kilo. The X-axis
7 is the age.

8 What is shown here is the median age and age
9 range in each treatment group. The Y-axis is the
10 mean Cmax. The green lines are the adult Cmax
11 reference value from the currently proposed OTC
12 monograph dose, high in 1,000 milligrams, low in
13 325 milligrams.

14 The red dotted lines are the age cutoffs,
15 6 months, 2 years and 12 years. These two graphs
16 show that the Cmax normalized to 10 or 15
17 milligrams per kilo in pediatrics is within the
18 Cmax range in adults given the currently proposed
19 OTC monograph dose.

20 This slide summarizes the AUC normalized to
21 10 and 15 milligrams per kilo. Same as the last
22 slide, the X-axis is the age, median age and age

1 range in each treatment group, and a mean AUC. The
2 green reference lines are the adult AUC value after
3 the 1,000 milligram and 325 milligram, and the red
4 dotted lines are, again, the age cutoff.

5 These two graphs show that the AUC
6 normalized to 10 or 15 milligrams per kilo in
7 pediatrics is also within the AUC range in adults
8 given the currently proposed OTC monograph dose.

9 To summarize this PK section, the exposure
10 of acetaminophen in pediatric patients given 10 to
11 15 milligrams per kilo orally is within the range
12 noted in the adult subjects given the proposed OTC
13 monograph dose.

14 Now, I will move on to discuss the dose-
15 response relationship for fever reduction of
16 acetaminophen in pediatric patients. In my
17 analysis, I will focus on the dose-response
18 relationship for fever reduction that included
19 patients less than 2 years of age.

20 To evaluate acetaminophen antipyretic effect
21 in pediatric patients, we reviewed published
22 literature on acetaminophen. Our literature search

1 focused on studies that included pediatrics less
2 than 2 years of age. In other words, studies with
3 the lowest pediatric age of 2 years and above were
4 not included. Subjects were given oral dose either
5 as a single dose or multiple doses, with dosing
6 intervals every six hours. Studies must have
7 available mean temperature versus time data up to
8 six hours post-dose.

9 Based on these criteria, we identified 15
10 main publications. This combined database includes
11 pediatrics aged between 2 months to 12 years, as
12 adequate data investigating the dose-response
13 relationship in age group of 6 months to 3 years of
14 age were not available.

15 Studies that included pediatric patients
16 below 2 years of age along with older pediatric
17 patients were reviewed. The oral dose of 5 to
18 30 milligrams per kilo were administered. The
19 patients were all with fever due to a variety of
20 reasons.

21 A typical concentration time profile on the
22 top and a fever reduction time profile at the

1 bottom are shown here in this slide. After oral
2 dosing, there is a delay in the time course of
3 antipyretic effect compared with the
4 pharmacokinetic profile. The delay in the
5 pharmacodynamic response to acetaminophen
6 presumably reflected the time taken for drug
7 transfer to effect compartments around the central
8 compartment in the response time.

9 To assess fever reduction, we used the
10 endpoint called weighted sum of temperature
11 reduction in six hours, briefly speaking, WSTD6, in
12 our analysis. Clearly, from the plot of WSTD6
13 versus dose, the fever reduction for acetaminophen
14 is dose dependent, with higher dose associated with
15 higher response.

16 If we focus on the dose range of 10 to
17 15 milligrams per kilo, the average temperature
18 reduction, calculated as this value, WSTD6, divided
19 by six is .7 to 1.5 degrees Celsius, whereas the
20 temperature reduction in the placebo group is less
21 than .25 degrees Celsius. However, since most of
22 these studies have an unknown number of patients

1 below 2 years of age, these studies should be
2 interpreted with caution with regard to the
3 applicability of these conclusions to pediatric
4 patients in age group of 6 months to 2 years.

5 To summarize this section, a delay of the
6 onset of maximum effect was observed in the fever
7 reduction for acetaminophen. Fever reduction is
8 dose dependent for acetaminophen in pediatric
9 patients, with the caveat in our analysis that the
10 number of patients between 6 months and 2 years is
11 not available. The average temperature reduction
12 in six hours is .7 to 1.5 degrees Celsius for 10 to
13 15 milligrams per kilo and less than .25 degrees
14 Celsius for the placebo group.

15 To conclude, as the contributing enzyme
16 CYP2E1 for toxic reactive intermediate NAPQI
17 formation is immature in younger pediatrics.
18 Neonates and infants may be less susceptible to the
19 reactive intermediate NAPQI associated liver
20 toxicity. Exposure of acetaminophen in pediatric
21 patients given 10 to 15 milligrams per kilo orally
22 is within the exposure range in adults given the

1 proposed OTC monograph dose. Acetaminophen dose of
2 10 to 15 milligrams per kilo appeared to be
3 efficacious in fever reduction in pediatric
4 patients in the age range of 2 months to 12 years.

5 Thank you for your time.

6 DR. NEILL: So in consultation with my co-
7 chair, I think what we're going to do is go ahead
8 and proceed with the presentation by Dr. Filie, and
9 then I understand Dr. Mathis has joined us, and,
10 Dr. Mathis, we'll look for your talk after.

11 Normally, we would have questions between each of
12 these groups. We're going to save those questions.
13 Please write them down. And at the end of each of
14 the four, as a block, we'll have time for questions
15 before our break.

16 Dr. Filie?

17 **FDA Presentation - Jane Filie**

18 DR. FILIE: Good morning. I'm Jane Filie,
19 and I will present a literature review of the
20 efficacy and safety of acetaminophen in children
21 6 months to 2 years of age. I will talk about the
22 literature search, followed by a summary of the

1 trials and their results, and I will conclude with
2 an overall summary.

3 I will first present data of acetaminophen
4 as an antipyretic. Fever is a symptom that
5 frequently drives parents to seek medical
6 attention. It is estimated that fever may account
7 for approximately one-third of all the presenting
8 conditions in children. It is most commonly
9 associated with infections, but may also occur with
10 immunizations, inflammatory diseases, and
11 malignancies.

12 Fever does not necessarily need to be
13 reduced to normal as it has beneficial effects in
14 fighting infection. According to the recently
15 published clinical report on fever and antipyretic
16 use in children by the American Academy of
17 Pediatrics, parents should treat fever to improve
18 the child's comfort while maintaining hydration and
19 observing for signs of serious illness. The main
20 goal of treating fever should be to reduce
21 discomfort and insensible water losses.

22 We searched for published trials in the

1 English language, focusing on those that provided
2 data on the antipyretic efficacy of oral
3 acetaminophen up to the dose of 15 milligrams per
4 kilogram per dose, as the proposed dosing ranges
5 from 10 to 15 milligrams per kilogram.

6 We also focused on the age range of 6 months
7 to 2 years of age. As you might know, there is now
8 an approved intravenous acetaminophen labeled for
9 use down to age 2 based on extrapolation of
10 efficacy for acute pain and fever reduction from
11 adult studies.

12 We excluded from the review trials that
13 utilized routes of administration other than the
14 oral route, use of prodrug, trials that used
15 loading doses of acetaminophen or that studied the
16 efficacy of regimens alternating acetaminophen with
17 other antipyretic, unless the trial provided
18 efficacy data of acetaminophen when used alone.

19 The search identified 51 fever trials, of
20 which 25 were reviewed. There were five placebo-
21 controlled, 14 active-controlled, and six comparing
22 acetaminophen to physical methods of cooling. The

1 physical methods of cooling included sponging and
2 clothing removal, and these trials were included in
3 the review because although not true placebo-
4 controlled trials, acetaminophen was not being
5 compared to another pharmacological agent, but to
6 an intervention. The remaining 26 trials were not
7 included because they either had an insufficient
8 number of children in the target population, lacked
9 a measure of temperature change, or provided
10 insufficient information to conduct a review and
11 assessment.

12 One of the challenges was to identify trials
13 that contained efficacy data on the target
14 population. The trials were not designed to
15 evaluate efficacy in children 6 months to 2 years
16 of age specifically, but this population was
17 included as part of a larger pediatric population.

18 Some trials had information on the number of
19 children in our target population, but most did not
20 provide such information. Therefore, the
21 population we were looking for had to be estimated
22 based on the number of children enrolled and the

1 mean ages.

2 The trials differed among themselves in
3 terms of design and methodology applied. Some
4 controlled for variables that may influence body
5 temperature, such as room temperature, the amount
6 of clothing, and oral intake. Some trials utilized
7 rectal thermometry, which is a gold standard for
8 the evaluation of body temperature, whereas others
9 utilized axillary and tympanic thermometry, which
10 are not as accurate for such assessment.

11 Some trials were conducted in the inpatient
12 setting, where study personnel, as investigators
13 and research nurses, monitored and treated the
14 patients, whereas some trials relied on the
15 parents' monitoring of the patients and recording
16 of the data, which may influence the reliability of
17 the data.

18 The children enrolled had a range of
19 underlying medical conditions. Some trials only
20 enrolled children with conditions that are commonly
21 treated in the community, while other trials
22 included children with more severe illnesses that

1 eventually led to hospitalization.

2 The timing of the assessments varied, as
3 well as the duration of the observations, which may
4 influence comparisons. For example, assessments at
5 30 minutes after dosing may be too soon for
6 medication to work and depending on the time of
7 maximal effect of a drug, an assessment made
8 earlier or later may favor a drug over another.
9 Most trials evaluated a single dose of antipyretic
10 treatment. Few of them evaluated multiple doses.

11 Lastly, the comparisons also varied in terms
12 of the doses and the comparator drugs. Not always
13 the lowest acetaminophen dose of 10 milligrams per
14 kilogram was compared to the lowest approved dose
15 of the comparator and vice versa. Acetaminophen
16 was also compared to unapproved drugs for which an
17 adequate pediatric dose has not been established.

18 The trials also evaluated the antipyretic
19 effect of acetaminophen by utilizing several
20 endpoints. The selected trials included measures
21 of temperature reduction, such as the mean change
22 in temperature from baseline, maximal temperature

1 reduction, and the area under the curve of
2 temperature change, among others. Few trials
3 attempted to assess improvement of comfort, but the
4 interpretation of this outcome is challenging given
5 the lack of validated assessment tools in the
6 pediatric population for this outcome.

7 Now, let's talk about the trials. There
8 were five placebo-controlled trials. All placebo-
9 controlled trials were randomized. Two were
10 double-blind and three were partial-blind. Two of
11 the five placebo-controlled trials included an
12 active control in addition to placebo, ibuprofen in
13 one trial and indomethacin in another. Four of the
14 trials utilized rectal thermometry and one
15 axillary.

16 The studies included children from 0 to
17 14 years of age overall. One of the challenges was
18 to assess whether the population between 6 months
19 and 2 years of age was adequately represented in
20 these trials. Four of the trials did provide some
21 information on the number of children in the target
22 population, and of the 845 children enrolled in

1 these trials, an estimated 40 percent were in the
2 target population.

3 In the five placebo-controlled trials,
4 acetaminophen was superior to placebo. It is
5 noteworthy that one of these trials was age-based
6 and that the acetaminophen dose averaged
7 7 milligrams per kilogram. A mean temperature
8 reduction of at least .8 degrees Celsius was
9 observed across the studies.

10 Here is one example of the antipyretic
11 response from an active and placebo-controlled
12 trial. The upper line represents the placebo
13 group. We can see clear separation of placebo from
14 the active treatments, including acetaminophen,
15 represented by the solid line right here. The
16 smaller graph to the left shows the treatment
17 effect after subtraction of the placebo response,
18 showing an approximately 1 degree Celsius effect
19 for acetaminophen.

20 Now, the active-controlled trials.
21 Acetaminophen was not superior to the active
22 comparator in any of the active-controlled trials,

1 although there were some comparators that were
2 superior to acetaminophen.

3 Although decreases in temperature were
4 observed in the acetaminophen treatment arms, these
5 trials cannot support the antipyretic effect of
6 acetaminophen because there was no placebo arm to
7 confer assay sensitivity to these trials.

8 Now, there were six trials in which
9 acetaminophen was compared to physical methods of
10 cooling. Four trials compared acetaminophen to
11 sponging, one compared acetaminophen to unclothing,
12 and three trials compared acetaminophen alone to
13 the combination of acetaminophen plus sponging.
14 The age range across the studies was 6 weeks to
15 12 years of age. Three of the trials utilized
16 rectal thermometry and three axillary.

17 These trials demonstrated that acetaminophen
18 was superior to unclothing and sponging alone, but
19 not to the combination of acetaminophen with a
20 physical method of cooling. Although not blinded
21 trials, because temperature is an objective
22 measure, the comparison of acetaminophen to a non-

1 pharmacological intervention provided some support
2 of the antipyretic effect of acetaminophen, showing
3 a temperature reduction of at least 1 degree
4 Celsius from baseline.

5 This is an example of the effect of
6 acetaminophen, represented by the closed triangles
7 here, relative to sponging, represented by the open
8 circles. There is clear evidence of antipyretic
9 efficacy after the first hour. Dosing was by
10 weight and included acetaminophen at 15 milligrams
11 per kilogram.

12 Now, I will talk about the analgesia trials.
13 The over-the-counter analgesic indication for
14 acetaminophen is the treatment of minor aches and
15 pains. The most common causes of acute pain in
16 children in the over-the-counter setting are
17 illnesses such as otitis media and pharyngitis and
18 minor trauma sustained from normal daily activity.

19 The literature search identified 10 pain
20 trials within our established specifications and
21 within the dosing range of 10 to 15 milligrams per
22 kilogram. There were four placebo-controlled

1 trials, five active control, and one trial
2 comparing acetaminophen to no intervention, which
3 was not a true placebo arm, but there was no
4 comparison to another pharmacological agent and, in
5 this case, not even to an intervention.

6 There were trials in which doses of
7 acetaminophen greater than 15 milligrams per
8 kilogram were studied. I will present information
9 for the trials that included a 10 to 15 milligram
10 per kilogram dosing range, because that is what is
11 under consideration.

12 Of the 10 trials, one studied the effect of
13 acetaminophen in nonsurgical pain, and nine studied
14 the effect of acetaminophen in post-operative pain,
15 and I will describe briefly the trials.

16 The one trial that evaluated nonsurgical
17 pain was a randomized, double-blind, placebo-
18 controlled trial that studied the analgesic effect
19 of acetaminophen in children with otalgia who were
20 being treated with an antibiotic for otitis media.
21 Ibuprofen was used as an active control, and the
22 trial included children 1 to 6 years of age.

1 In this trial, the active comparator was
2 superior to placebo, but not acetaminophen. There
3 was, however, a numerical difference in the
4 proportion of children who had otalgia two days
5 after initiation of therapy, showing a trend in
6 favor of acetaminophen. In this trial, pain was
7 measured using a course outcome measure, such as
8 pain or no pain or ear-pulling, and perhaps was not
9 sensitive enough to detect the treatment effect of
10 acetaminophen.

11 Of the remaining nine trials that studied
12 post-operative pain, three were randomized, double-
13 blind, placebo-controlled, and they all included an
14 active comparator, either ibuprofen, ketorolac, or
15 acetaminophen plus codeine. The latter two drugs
16 are not approved for use in children younger than
17 2 years of age.

18 The children received the analgesic 30 to
19 60 minutes prior to anesthesia induction, and they
20 all underwent bilateral myringotomy for tympanic
21 tube placement. The outcome measures were mean
22 pain scores in the post-anesthesia care unit and

1 need for rescue analgesia.

2 None of the three placebo-controlled trials
3 demonstrated superiority of acetaminophen
4 statistically. In one trial, all patients received
5 eardrops with lidocaine interoperatively, which may
6 have masked the effect of acetaminophen.

7 Another trial showed an effect size of 1 to
8 2 on a 0 to 10 pain scale and a numerical
9 difference in the need for rescue analgesia.
10 Although it did not achieve statistical
11 significance, it showed a trend in favor of
12 acetaminophen.

13 Of the remaining six trials that studied the
14 analgesic effect of acetaminophen in the post-
15 operative setting, five were randomized, double or
16 observer-blinded and had an active control, but no
17 placebo control. One of the trials did not provide
18 sufficient information.

19 The trials included children 6 months to
20 9 years of age, and the mean age was approximately
21 2. The comparators included acetaminophen with
22 codeine, diclofenac, ketorolac, and transnasal

1 butorphanol. The analgesics were given 20 to
2 60 minutes prior to anesthesia induction. The
3 outcome measures were mean pain scores in the post-
4 anesthesia care unit and need for rescue
5 medication.

6 None of the active control trials
7 demonstrated superiority of acetaminophen over the
8 comparators. In one of the trials, all patients
9 received fentanyl intraoperatively, which may have
10 masked the effect of acetaminophen.

11 Lastly, the remaining pain trial was
12 randomized, open label, and observer-blinded. The
13 trial included children 1 to 5 years old who
14 underwent bilateral myringotomy for tympanic tube
15 placement. Although it was available only as an
16 abstract, it provided some information regarding
17 the analgesic effect of acetaminophen.

18 One group received oral acetaminophen
19 30 minutes prior to anesthesia induction, while
20 another group received no preoperative treatment,
21 and another group received rectal acetaminophen in
22 the immediate postoperative period as an active

1 comparator. The outcome measures were, again,
2 postoperative pain scores in the post-anesthesia
3 care unit and need for rescue medication.

4 Oral acetaminophen given preoperatively was
5 superior to the active comparator, rectal
6 acetaminophen, and superior to no treatment. I
7 defer any discussion of the statistical
8 significance of the data, as we cannot confirm the
9 statistical analyses conform to our standards.

10 In terms of safety data, few events were
11 reported in the single-dose trials and they were
12 mild to moderate in severity. The most common
13 adverse events reported were nausea, vomiting,
14 rash, and hypothermia. The multiple dose trials
15 did not provide sufficient safety information.

16 In summary, overall, the data is supportive
17 of the antipyretic effect of oral acetaminophen at
18 the dose of 10 to 15 milligram per kilogram in the
19 population studied. With respect to the pain
20 trials, the data found in the literature were
21 limited. The efficacy data in one placebo-
22 controlled trial was measured using a course

1 outcome measure that perhaps could not detect
2 smaller degrees of pain relief. In the other
3 trials, analgesia was given prior to the procedure,
4 and results may have been confounded by the use of
5 interoperative medications.

6 There is, however, limited evidence to
7 support the analgesic effect of oral acetaminophen
8 at the dose of 10 to 15 milligrams per kilogram in
9 the patient population studied based on numerical
10 differences in pain scores and need for rescue
11 medication.

12 Thank you.

13 DR. NEILL: So, Dr. Mathis, if you're ready,
14 we're going to jump back and discuss extrapolation
15 and then have time for questions.

16 **FDA Presentation - Lisa Mathis**

17 DR. MATHIS: Hi. Thank you very much. And
18 first of all, my apologies for being tardy this
19 morning and thank you to the chair for being so
20 flexible and allowing me to come now.

21 So today I'm briefly going to go over a
22 review of extrapolation, talking about what it is

1 and why we use it. So, first, I'm going to start
2 out with a definition of extrapolation, which can
3 be found, amongst other places, in the Pediatric
4 Research Equity Act of 2007.

5 So if scientific data supports that the
6 course of the disease and the response to therapy
7 are sufficiently similar in adults and children,
8 then efficacy can be extrapolated from adequate and
9 well-controlled studies in adults to the pediatric
10 population. Now, this extrapolation is usually
11 supported with additional data in pharmacokinetics
12 or safety or other studies, as well.

13 Extrapolation only applies to efficacy. The
14 dose cannot be extrapolated and neither can safety.
15 This is really important to remember, because we
16 know that absorption, distribution, metabolism and
17 elimination in pediatric patients is different from
18 adults, and this is based on developmental
19 differences. And these developmental differences
20 also contribute to unique safety adverse events
21 that we see in the pediatric population, as well.
22 So, again, we can extrapolate efficacy, but we

1 cannot extrapolate safety or dosing.

2 As an example of extrapolation, we have the
3 product Ofirmev, which is IV acetaminophen.

4 Dr. Filie just mentioned this product. It was
5 approved in 2010 for the treatment of -- management
6 of moderate to severe pain and also reduction of
7 fever in patients 2 years of age and older.

8 Because of the similarity of the underlying
9 painful conditions and the metabolic pathways that
10 contribute to the metabolism of acetaminophen,
11 efficacy was extrapolated from the adult population
12 down to age 2. Now, we don't believe that the
13 mechanisms in patients younger than 2 are the same,
14 so we didn't allow extrapolation less than age 2.
15 But we also obtained additional safety and
16 pharmacokinetic data from pediatric patients. Over
17 300 patients were looked at all the way down to
18 birth.

19 So why do we extrapolate? Well, oftentimes,
20 in pediatrics, there are a limited number of
21 pediatric patients to study, to enroll in studies.
22 So extrapolation allows us to obtain adequate data

1 in order to label a product for use in the
2 pediatric population. And while this is really
3 important, it is not the most important reason for
4 us to extrapolate. Really, the most important
5 reason for us to extrapolate is more from an
6 ethical perspective. It's not really appropriate
7 to study pediatric patients when we already know
8 the answer to the question.

9 Children are vulnerable and they require
10 additional safeguards in studies. They can't often
11 communicate their feelings or symptoms, and because
12 they're less than legal age, they also can't
13 legally consent to be in trials, although their
14 parents can consent for them and they can assent.

15 So because of the fact that they are
16 vulnerable, the real reason to extrapolate is
17 because if you already know that the product works
18 based on scientific data, then there's no reason to
19 repeat studies with those pediatric patients.

20 So, in conclusion, extrapolation is an
21 important tool for us to increase the efficiency of
22 pediatric drug development and, more importantly,

1 to avoid unnecessary trials in that same
2 population. And it should be used whenever
3 possible because it allows us to better utilize
4 limited resources, limit exposure to children in
5 unnecessary trials, and also allows us to obtain
6 results much sooner and expedites access to
7 medication for pediatric patients.

8 That's it. I promised it was going to be
9 brief.

10 DR. NEILL: I am from Philadelphia, and that
11 makes me a baseball fan. Over the years, I've
12 learned that the one key to success in singing the
13 National Anthem is speed.

14 [Laughter.]

15 **Clarifying Questions**

16 DR. NEILL: So I appreciate that we are
17 ahead of schedule. In part, that's because we've
18 combined two different breaks for questions. I am
19 not a pharmacist and my days of pharmacokinetics
20 are way behind me, so I could fill probably most of
21 the session with questions.

22 But I'd like to take time now for advisory

1 committee members that have clarifying questions
2 for any of the four presenters, to ask those now.
3 If you could raise your hand, and I will try and
4 recognize you in turn as we go around.

5 Dr. Farber?

6 DR. FARBER: So, first of all, I would just
7 like to say go Phillies.

8 [Laughter.]

9 DR. NEILL: Thank you.

10 DR. FARBER: I have several questions, but
11 of different presenters, but I'll ask one in
12 deference to the fact that I'll take my turns
13 later.

14 So for Dr. Filie, I have two questions for
15 you, actually. One is you state that there is
16 limited evidence to support the use of
17 acetaminophen for pain in children from 6 months to
18 2 years.

19 I'm questioning what limited evidence you're
20 referring to, since what I gleaned from your
21 presentation is that of the 15 studies, only one
22 showed any kind of efficacy, and that was one that

1 was not placebo-controlled.

2 Are you referring only to that one or are
3 you referring to the others that showed a trend,
4 but no statistical significance?

5 The other question I have is regarding
6 analysis of the studies looking at fever reduction
7 in response to acetaminophen. I'm wondering if
8 anybody has attempted to do a meta-analysis to see
9 if specifically the children aged 6 months to
10 2 years respond appropriately.

11 DR. FILIE: I'm here, Dr. Farber.

12 With respect to the first question, yes, I
13 meant that the evidence in the literature is
14 limited to support the pain effect on children
15 6 months to 2 years of age for the reasons that I
16 mentioned. First of all, we cannot tell for sure
17 that those trials had a large number of patients in
18 the population that we would like to see. And of
19 the trials that I reviewed, the difference was not
20 statistically significant in any of those trials.
21 But there is some numerical difference between pain
22 and placebo and the difference in need for rescue

1 medication. These differences, again, did not
2 achieve statistical significance, but it is a
3 trend. That's all I can say.

4 Dr. Hertz might want to say something.

5 DR. HERTZ: So, basically, yes, we agree
6 that based on what we were able to find in the
7 literature, there's really not adequate support.
8 There's a real dichotomy, we think, between what
9 was available for fever versus what was available
10 for pain.

11 DR. FARBER: I wanted to make sure you were
12 saying there was not adequate support rather than
13 there is limited support.

14 DR. HERTZ: Yes, limited.

15 DR. FILIE: And with regard to the fever
16 question, could you repeat, please?

17 DR. FARBER: Yes. Has anybody attempted to
18 do a meta-analysis to see if the 40 percent of the
19 845 children included in those trials, the age
20 group in question specifically responded
21 appropriately? Has anybody done a meta-analysis?

22 DR. FILIE: Not specifically for the age

1 group 6 months to 2 years of age. Again, this is
2 all based on estimates. And of the trials that I
3 presented, especially the placebo-controlled
4 trials, I could find those numbers. I can assure
5 you that at least 40 percent of the children in
6 those placebo-controlled trials are within the
7 range of 6 months to 2 years, but, again, it's
8 estimated.

9 DR. HERTZ: Just if I might add. From those
10 papers, there wasn't a lot of information from
11 which a meta-analysis could actually be conducted
12 for a sub-population. We did not attempt to go
13 back to the authors or anything to get additional
14 info.

15 DR. NEILL: So I'm reminded that for each of
16 you that are asking questions and responding,
17 before you speak, please state your name.

18 Dr. Griffin next, and then Dr. Parker.

19 DR. GRIFFIN: We heard a little bit about
20 extrapolating efficacy, and I'm wondering, for the
21 pain, is it possible to extrapolate efficacy for
22 pain from older children or from adults? How did

1 you interpret the literature on that?

2 DR. HERTZ: So this is a really good
3 question, and it's one that we struggle with in
4 general, I think, in many therapeutic areas.

5 DR. NEILL: Could you state your name?

6 DR. HERTZ: Sorry. Sharon Hertz, FDA. You
7 think I would know by now with all these meetings.

8 So it is something that we struggle with.
9 And we've actually, about a year and a half ago,
10 conducted a meeting with a number of pediatric
11 analgesic people from academia to try and sort out
12 some of this. And exactly when it is appropriate
13 to extrapolate; to what extent; how does that work;
14 what drugs?

15 We're working on that now. We're going to
16 hopefully come out with guidance. I think that
17 there should be a paper sometime soon that
18 summarizes the thinking of the group that was asked
19 to comment. And right now, what we're tending to
20 do is extrapolate down to age 2 based on the advice
21 and our own readings of what's available.

22 So for analgesics, we're extrapolating, for

1 the most part, down to age 2 with products that
2 have relatively well known mechanisms of action or
3 a lot of information; so, for instance, opioids,
4 NSAIDs. We are asking for information below the
5 age of 2. I think at some point in time, that
6 could change, but for now that's our current
7 approach, and for acetaminophen.

8 DR. NEILL: Dr. Parker?

9 DR. PARKER: I think this goes to Dr.
10 Furness, just sort of a clarification. Starting
11 with sort of the big picture, if we look at -- and
12 this has to do with single ingredient versus combo
13 products and taking sort of the consumer
14 perspective on that.

15 If we look at how many acetaminophen
16 products there are on the market, we know that
17 maybe a little over half of them are single
18 ingredient. If we look just at pediatric liquid
19 formulations using the database that we used in the
20 JAMA piece that was published late last year at
21 liquid formulations, top 200 selling products, it
22 represented over 99 percent of the market that

1 consumers face.

2 There were 39 products in that that
3 contained acetaminophen. Most of those are combo
4 products. And if we look specifically at how many
5 of those had anything on the carton relating to
6 children under 2, consult your doctor, those are
7 all single ingredient products.

8 But going back to the central question, the
9 slide that he put up, what is the key question that
10 frames where we're going in the whole meeting, are
11 the existing dosing directions and age breakdowns
12 sufficient to apparently administer OTC
13 acetaminophen-containing drug products, I'm really
14 trying to step back and look at what consumers face
15 when they walk in and see these shelves and look at
16 them and try to figure out. We also have ongoing
17 studies that show us that people really don't know
18 what they're taking.

19 So from a public health standpoint and from
20 the purview of the regulatory agency with public
21 health as its mission, I'm really wondering about
22 how we think of this looking only at single

1 ingredient products when consumers face a market
2 that has so many combination products.

3 I know that those under 2, if we limit
4 ourselves to the ones that are under 2, are single
5 ingredient. But for consumers, this is really hard
6 to sort out. So I just wanted a little clarity
7 from the agency about how we think about this since
8 this is sort of, in the interest of public health,
9 where the public turns for safety on that.

10 DR. NEILL: Dr. Furness or staff?

11 DR. FURNESS: Your point is very well taken
12 about the combination products versus the single
13 ingredient products. This meeting, as we said
14 earlier, is focusing on the single ingredient
15 products. Obviously, if we were to do some of the
16 proposals we're contemplating for the multi-
17 ingredient products, we would need that much more
18 data for each of the combos.

19 DR. PARKER: One other clarity question is
20 just that all the studies that were presented about
21 the pharmacodynamics, those all relate to single
22 ingredient products rather than combo, knowing that

1 the market mostly reflects combination products, I
2 take it, which is what people would actually be
3 taking in real life. Is that correct?

4 DR. KWEDER: I can answer that. Yes, but in
5 order to address combination products, you have to
6 start with the single ingredients. And that's why
7 we're not talking about combination products today.

8 The combination products are usually
9 combinations of ingredients to treat different
10 things. In most of those combinations, you're not
11 seeing, for example, two products to address fever
12 or two products to address analgesia in
13 combination. They're to treat different symptoms,
14 and the different ingredients are targeted to the
15 different symptoms.

16 The only way we can affect a change in some
17 of the combinations is to march through the single
18 ingredients, and that's why we're focusing on this
19 one today. We can't address the full scope of the
20 combinations until we've focused on the single
21 ingredients. At least we can't bring science to
22 the combinations.

1 DR. NEILL: So I'm going to ask folks again
2 to try and remember to state your name beforehand.
3 It makes it easier for the transcriptionists when
4 they're typing to know who it was that was
5 speaking.

6 I have Dr. Reidenberg and Dr. Rosenthal.
7 Dr. Reidenberg?

8 DR. REIDENBERG: A question for Dr. Filie.
9 Most of the pain studies, as I looked at them, had
10 active comparators that had no capacity to show
11 that acetaminophen was better.

12 Which of the studies were a protocol that
13 actually had a realistic capacity to show that
14 acetaminophen could relieve pain?

15 DR. FILIE: I'll have to defer that to
16 Dr. Hertz.

17 DR. HERTZ: I'm sorry. Could you just
18 restate that question?

19 DR. REIDENBERG: Yes. As I went over the
20 analgesic studies, most of them were set up so that
21 realistically they had no capacity to show that
22 acetaminophen relieved pain, if we're comparing it

1 with ibuprofen or an opioid.

2 DR. HERTZ: Right.

3 DR. REIDENBERG: And so as I recall, there
4 are only one or two studies in the whole group that
5 had a protocol that actually had the capacity to
6 show analgesic effect, if it was there, and that
7 most of the others were unable to answer the
8 question that you were trying to have them answer.

9 DR. HERTZ: Exactly. This is Sharon Hertz.
10 And that's the problem. We tried to present what's
11 available, and I think that this does highlight
12 that there's a real gap in this particular area.

13 I think that the contrast between having
14 those nice fever curves and those response curves
15 for the fever indication, and you saw no data
16 presented for the acetaminophen because it was so
17 limited, it was just a way to underscore that there
18 is a gap.

19 I think that had we presented nothing, we
20 would have been asked, "is there nothing," and
21 there was something, it was just very, very weak.

22 DR. NEILL: Dr. Rosenthal?

1 DR. ROSENTHAL: This is Jeff Rosenthal. I
2 have two questions on disparate topics. One is
3 pertaining to extrapolation.

4 My question is, does the agency think about
5 extrapolation the same for products regulated under
6 the NDA process and those that come under the
7 monograph process?

8 DR. MURPHY: Yes. Dianne Murphy.

9 DR. ROSENTHAL: Okay. The next question is
10 on the topic of metabolism.

11 Dr. Ji, you showed some information about,
12 first, that it seems like the oxidative metabolites
13 are the ones that we should be most focused on, and
14 then also you nicely showed that there are
15 developmental differences in the metabolic
16 pathways. And it seems as though, from the
17 information that we've seen, that there should be a
18 very low risk of hepatotoxicity in neonates even at
19 high doses, given what's been shown.

20 Can you just clarify? Is that practically
21 true, theoretically true, or have I misinterpreted
22 the information that's been presented?

1 DR. JI: Yes. Theoretically, it is true.
2 In neonates and infants, they do have less CYP2E1
3 protein expression as compared to older pediatrics
4 and adults. And I also presented one published
5 paper by van der Marel in 2003. They tried to
6 monitor the oxidative downstream -- metabolites and
7 they could not measure it.

8 DR. ROSENTHAL: Rosenthal with a follow-up.
9 Then I would be correct to infer that concerns
10 about safety in neonates should be pretty small.

11 DR. JI: Yes.

12 DR. ROSENTHAL: Do you know whether this is
13 true in practice, as well as in theory?

14 DR. JI: In practice, you will also hear
15 from later presenters that they will present some
16 summary from the AERS database. You can see how
17 much, from the epidemiology perspective, what is
18 the hepatotoxicity risk in neonates, in pediatrics.

19 DR. ROSENTHAL: Thank you.

20 DR. NEILL: So I've got a question that I
21 think is for Dr. Filie. Dr. Mathis discussed the
22 process of extrapolation from adult to pediatric

1 data. And I haven't been involved in a lot of
2 meetings where that concept was discussed, and the
3 phrase "response to therapy," so extrapolation when
4 the course of the disease and the response to
5 therapy are similar.

6 I'm struck that the discussion of the
7 analgesia study specifically include responses to
8 therapy primarily in surgical patients and I
9 gather, in those that are youngest, using a pain
10 score that uses grimacing or posturing or some
11 other things. I'm not familiar with those kinds of
12 scores. I'm imagining.

13 I wonder if you could discuss, in those
14 studies, what types of response to therapy were
15 measured. How? Was it with that kind of
16 behavioral score? And if so, how can that guide
17 the committee in a discussion, given the paucity of
18 data about analgesia, in our discussion today and
19 tomorrow?

20 DR. FILIE: I'll just give an introduction.
21 Probably Dr. Hertz will chime in. That is actually
22 a challenge. These pain trials did utilize

1 different pain measurement scores, one called
2 objective pain scale, the other one is the
3 Children's Hospital Eastern Ontario pain scale.

4 So these are all based on behavior changes
5 and grimacing. And we're still not sure -- as
6 Dr. Hertz said, we're still kind of coming
7 together, trying to see how effectively we can
8 evaluate pain in these younger populations. So
9 that is one challenge of the literature review that
10 we did. I don't know if Dr. Hertz wants to add
11 anything to this.

12 DR. HERTZ: So a number of people have
13 developed different measures to evaluate pain in
14 preverbal, nonverbal age range, and they are
15 difficult. And I think part of the reason why
16 there's a paucity of good studies, not that these
17 are bad studies, but what we would consider
18 adequate and well-controlled studies in the
19 literature, is because these are very difficult to
20 do. Fever, as Dr. Filie mentioned, doesn't always
21 need to be treated, and the use of a placebo or
22 non-pharmacologic measures is generally not

1 considered unethical, depending on the situation.

2 Treating pain is a little different because
3 there's less tolerance for not treating pain.

4 Family members are less interested in giving
5 consent if there is a option that their child will
6 not be treated. This is not just in the very
7 youngest age range. This is the entire pediatric
8 age range. And as a result, we tend to see studies
9 that don't necessarily give us the type of data
10 that we can use for a regulatory decision. So
11 there's a lot of active-controlled studies. But we
12 know in pain, showing that two products are similar
13 means they either both work or they both don't
14 work. And when you add in the challenge of the
15 difficulty in measuring a subjective measure in
16 nonverbal patients, it's very, very challenging.

17 That was part of why we asked for help from
18 the pediatric pain community to address some of
19 this, and we have some good advice that we've been
20 given to help move some of these studies forward in
21 terms of study design and how to proceed.

22 So in terms of your question how to guide

1 the committee, I think that when you start to
2 discuss whether you think there's enough
3 information, either based on the limited, also
4 could be referred to as inadequate data that was
5 presented, as well as what's known about efficacy
6 in older populations, if you decide that more
7 information is needed, then please advise us. If
8 you think not, please advise.

9 So that's the guide. We gave you what we
10 have. You let us know what your comfort is in
11 terms of different paths to follow with that.

12 DR. NEILL: As somebody who deals with a lot
13 of adult patients with chronic pain issues, I often
14 dream about patients that don't verbalize.

15 [Laughter.]

16 DR. NEILL: I've got Dr. Towbin and then
17 Dr. Walker-Harding and Dr. Reidenberg again.

18 Dr. Towbin?

19 DR. TOWBIN: Well, I was actually very taken
20 with Dr. Parker's comment and I kind of wanted to
21 follow-up on that just so that I understood about
22 the impact of the decision that we're asked to vote

1 on, and Dr. Kweder's reply.

2 If we answer the question related to
3 acetaminophen, what effect will that have on
4 combination products that may be combined with
5 things like caffeine or diphenhydramine or
6 dextromethorphan, when, in fact, the metabolic
7 pathways may be altered by those combination agents
8 and actually might influence some of the decisions
9 that we would have to make?

10 DR. KWEDER: The standards that are
11 developed for acetaminophen would be required to be
12 incorporated into its use in any combination
13 product, and that's the short answer.

14 So that's why it's extremely important.
15 Combinations are a different animal, but the key in
16 a monograph product is that you still have to
17 follow the monograph for the individual ingredient
18 in whatever combination is developed.

19 Does that help?

20 DR. TOWBIN: This is Dr. Towbin again. I
21 think it helps. I guess what I wonder about is how
22 the dosing is influenced by some of those

1 combinations.

2 DR. KWEDER: So your concern is about, like,
3 so what happens when you put it in combination
4 with, say, diphenhydramine or whatever else it
5 might be.

6 DR. TOWBIN: Indeed.

7 DR. KWEDER: And those really get into the
8 whole world of combinations and what's required for
9 combinations. It's extremely complicated,
10 extremely complicated. And, unfortunately, for NDA
11 products, it's much more straightforward than it is
12 for OTC monograph products, and we are dealing with
13 some of those other monographs separately. But our
14 goal ultimately is to assure that all of those
15 things get addressed, and one of the steps in doing
16 that is really understanding what an appropriate
17 dosage is for the individual ingredients.

18 So we still have a lot of work before us in
19 addressing the combinations, there is no question
20 about that. We're very appreciative of that fact.
21 But we think it's essential that we nail down the
22 issues with acetaminophen as part of that. So this

1 is one piece of a much bigger puzzle.

2 DR. NEILL: Dr. Walker-Harding?

3 DR. WALKER-HARDING: I had a question, and
4 I'm not sure who it should go to. But it was noted
5 that these were all English-written studies. Are
6 there any studies that were not in English looking
7 at the analgesic effects of acetaminophen in this
8 age group that could be translated?

9 DR. NEILL: Dr. Filie?

10 DR. FILIE: Yes. There were a few of them,
11 and just based on the abstracts in English, none of
12 them showed that acetaminophen was superior to the
13 comparator. I don't recall any of them being
14 placebo-controlled, though. I think they were all
15 active-controlled trials. And just based on the
16 abstracts, they did not show superiority, at least
17 of the ones that I encountered. There were a few,
18 maybe four or five, for fever, not for pain. I
19 don't remember recalling any pain trials; fever
20 trials.

21 DR. NEILL: Dr. Reidenberg and then
22 Dr. Kweder.

1 DR. REIDENBERG: I thought that Dr. Hertz's
2 review of the problems of this area was very
3 comprehensive. And it would help me if you could
4 at least give me a summary of the results of those
5 studies that actually had the capacity to show
6 acetaminophen had analgesic activity. Those with
7 the active comparators I don't think had that
8 capacity. And so it would be nice to see the
9 results of those that really could show the effect,
10 if it were there.

11 DR. HERTZ: I believe the one study that
12 Dr. Filie presented, where there was about a 1 to
13 2-point change on a numeric rating scale was pretty
14 much it. That didn't reach statistical
15 significance within that study. I think she's
16 checking her notes, but I don't think there was
17 much more than that.

18 DR. NEILL: Dr. Kweder?

19 DR. KWEDER: I just wanted to follow-up.
20 This is Sandy Kweder. I wanted to follow-up on the
21 previous question about combinations.

22 Many of you are quite familiar with all the

1 struggles we've had with cough and cold products,
2 and that stands for pediatric products, as well as
3 adults. And we are addressing and working on ways
4 to get data in on some of those products that will
5 speak to exactly these same issues, because
6 acetaminophen is -- those are some of the most
7 common ingredients in the combination products.

8 DR. NEILL: Dr. Parker?

9 DR. PARKER: So should we assume, as we look
10 at our agenda for the meeting, since we're looking
11 at all products that contain acetaminophen, that
12 the dosing of the acetaminophen products is the
13 most important part of the dosing of those
14 combination products? I'm just sort of thinking
15 about being a consumer, too, and if we can't figure
16 out how to read the label, how they're going to.

17 DR. FURNESS: I wouldn't say that the dosing
18 that we will arrive at, at this meeting, and any
19 new recommendations will play any greater factor
20 for acetaminophen versus the other combinations
21 that you may see out there.

22 DR. PARKER: And I say that because that's

1 the bulk of the market.

2 DR. NEILL: I haven't heard that the focus
3 of this meeting is on the multi-ingredient
4 products. Having said that, the focus on the
5 single ingredient products has, despite review
6 since 1988, we've not made process. And so I do
7 appreciate that in these meetings, staff take the
8 temperature, if you will, of the entire
9 conversation, and I'm confident that those comments
10 are going to be heard.

11 But we'll focus during this meeting on the
12 single ingredient and then hopefully move on. And
13 if past experience is any predictor, those of you
14 who share that interest will be asked to re-up your
15 membership on the committee and continue to work on
16 those.

17 [Laughter.]

18 DR. NEILL: Any other questions for any of
19 the speakers? Yes?

20 DR. WATTS: Dr. Watts. I have a quick
21 question. You spent a great deal of time looking
22 at the superiority of acetaminophen, but given the

1 ethical issues that were noted, and everything was
2 largely placebo, have you done any work looking at
3 equivalents of acetaminophen?

4 DR. HERTZ: We don't really have a way to do
5 that, because what we know with analgesic studies
6 in adults is that if you try a non-inferiority
7 study, you may be able to demonstrate that two
8 products are not inferior to one another. But you
9 could take either one of those products in a
10 placebo-controlled study and show that it fails,
11 even for known analgesics, because there are many
12 variables that can affect analgesic studies.

13 So, for instance, morphine, something as
14 basic as morphine can fail in some studies. So
15 that's a problem for us when it comes to trying to
16 develop assay sensitivity in an analgesic trial,
17 and, therefore, our requirement is -- our standard
18 is to require demonstration of superiority. It
19 does not have to be superiority against a placebo.
20 It could be a dose control, it could be an active
21 comparator. But we need some evidence that
22 something is actually working.

1 Pain, as you know, will fluctuate over time,
2 and then you add in the extra noise of challenging
3 measures in this age range. So then it becomes
4 even more difficult, because did the child fall
5 asleep because it was sedated, because the pain
6 went away, because somebody fed the child, changed
7 their diaper? It's extremely difficult to assess
8 pain, in general.

9 One of the approaches that we've been
10 advised to consider, and we are, is an add-on
11 design which would allow patients to receive pain
12 medication, all patients to receive pain
13 medication, and to use the drug of interest as
14 additional medication on top of that versus a
15 placebo, so that nobody is truly untreated. And
16 that gives us the opportunity to then look at the
17 impact of the add-on on the underlying drug use.

18 So, for instance, if you add drug B onto a
19 regimen where everyone is getting A, does the
20 amount of A get reduced? And, obviously, this
21 would not work with products that we don't have any
22 information on from adults. It wouldn't work for a

1 novel product, but we rarely would study a novel
2 analgesic in a pediatric population anyway.

3 So we're trying to adopt methods that would
4 allow these studies to be conducted, which is the
5 first hurdle, is actually getting them done, and
6 then also having them produce useful information.

7 So that's why the concept of
8 equivalence -- or, for us, it would be called non-
9 inferiority -- is troublesome in this therapeutic
10 area.

11 DR. NEILL: Dr. Notterman?

12 DR. NOTTERMAN: Dr. Hertz has very nicely
13 summarized some of the daunting issues with pain
14 studies in children. But I wonder if, in the
15 reviews of literature, you or your staff have had a
16 chance to look at studies in nonhuman animals in
17 terms of pain control.

18 Is there a signal at all that acetaminophen
19 is effective in some of those models? And do you
20 know if there have been studies using more modern
21 or innovative techniques, such as FMRI, in the
22 assessment of analgesic response to this agent?

1 DR. HERTZ: I'm going to assume you mean for
2 looking at perhaps the efficacy in juvenile
3 animals. I don't know that we would tend to
4 extrapolate that. We know how acetaminophen works
5 in adults and in older individuals. So we do have
6 some evidence, if you can consider that another
7 species, perhaps, but above the age of 2. But we
8 almost always look at nonclinical work in early in
9 development, but it's hard to know how to
10 extrapolate that in this setting. So I think we
11 would be better informed looking at the older
12 populations than, in this particular setting,
13 looking for a nonclinical model.

14 I'm sorry. I'm not remembering the second
15 part of that.

16 DR. NOTTERMAN: I was asking about more
17 recently developed assay tools, such as FMRI.

18 DR. HERTZ: We're following that, but, so
19 far, we have not seen its utility yet in this
20 particular niche. It's got a lot of promise. We'd
21 love to objective measures of some sort to evaluate
22 pain, but so far they haven't filtered into the

1 regulatory environment.

2 DR. NEILL: Dr. Santana?

3 DR. SANTANA: It's my understanding that on
4 occasion, some of these studies will require
5 consumer-directed understanding of the label and
6 dosing and how to self-prescribe and use it
7 appropriately.

8 Have there been any studies that we'll see
9 today where that has particularly been addressed
10 with parents dosing their children and following
11 some of the design algorithms that we saw today?
12 Is there any data on that or are we going to be
13 able to see that?

14 DR. FURNESS: This is Scott Furness. I'm
15 from the FDA. The Division of Medication Error and
16 Prevention Analysis may be presenting later on
17 today addressing that issue.

18 DR. NEILL: Anymore questions from the
19 committee?

20 [No response.]

21 DR. NEILL: So absent that, we're going to
22 take a short break. My watch says 6 minutes until.

1 So we're going to reconvene at 5 after 10:00, and,
2 for the record, we're still a little bit ahead.

3 For those of you on the committee, please
4 remember that you're not discuss the meeting topic
5 over the break. Thank you.

6 (Whereupon, a recess was taken.)

7 DR. FURNESS: So my watch says 11 after.
8 I'd like us to reconvene, please. I'm sorry. My
9 watch says 6 after. I still want to reconvene.

10 [Laughter.]

11 DR. FURNESS: So if Dr. Chan is present, I'd
12 like to restart things now with a presentation from
13 the Office of Surveillance and Epidemiology.

14 Dr. Chan?

15 **FDA Presentation - Irene Chan**

16 DR. CHAN: Good morning, ladies and
17 gentlemen. My name is Irene Chan, and I'm with the
18 Division of Medication Error Prevention and
19 Analysis.

20 The next set of presentations that you'll be
21 seeing this morning are provided by the Office of
22 Surveillance and Epidemiology. These presentations

1 will provide a public health perspective on
2 acetaminophen use in pediatric patients and some of
3 the consequences of that use.

4 These presentations will include
5 characterization of drug utilization trends,
6 hospitalization trends for acetaminophen poisoning
7 in children, examination of data from poison
8 control centers, as well as details from case
9 reports that were submitted to the agency. We have
10 also invited a guest speaker from the University of
11 Texas, who will be presenting on her research on
12 patient and caregiver knowledge of acetaminophen
13 use and dosing.

14 Our first presenter is Dr. Tracy Pham with
15 the Division of Epidemiology, and she will be
16 presenting on single ingredient acetaminophen
17 utilization in the United States.

18 **FDA Presentation - Tracy Pham**

19 DR. PHAM: Good morning. My name is Tracy
20 Pham. Today I will provide the analysis for the
21 use trends of OTC and prescription acetaminophen
22 products.

1 The outline of my presentation is as
2 follows. First, I will describe the sales and
3 outpatient prescription data of single ingredient
4 acetaminophen products. Then I will discuss the
5 limitation of the databases and summarize the
6 presentation.

7 We begin with the national over-the-counter
8 sales data. The IMS database was used to obtain
9 the total sales of OTC and prescription
10 acetaminophen products from year 2001 to year 2009.
11 The IMS database measures the volume of
12 prescription and OTC drug products sold in eaches
13 from manufacturers to retail and non-retail
14 channels of distribution, but does not provide
15 estimates of direct patient use of drug products.
16 Throughout the whole presentation, eaches refer to
17 the number of bottles, packets, or vials of a
18 product shipped in a unit.

19 Once again, it is important to understand
20 that these data do not provide a direct estimate of
21 patient use, but do provide a national estimate of
22 units sold from the manufacturer to various

1 channels of distribution.

2 From year 2001 to year 2009, the sale of OTC
3 and prescription acetaminophen products increased
4 by 38 percent. Around 338 million bottles of the
5 whole market were sold in year 2009. Of these, OTC
6 acetaminophen products accounted for 81 percent of
7 the total sale market. This amount breaks down to
8 58 percent for OTC combination and 42 percent for
9 OTC single ingredient acetaminophen products.
10 Prescription combination acetaminophen products
11 accounted for the remaining 19 percent of the total
12 sales.

13 Now, I will move on to a more detailed
14 analysis of OTC single ingredient acetaminophen
15 products. From year 2001 to year 2009, the sales
16 of OTC single ingredient acetaminophen products
17 increased by approximately 35 percent, with 151
18 million bottles sold in year 2009. Oral liquid
19 formulations made up around 25 percent of sales, of
20 which concentrated oral drops accounted for around
21 35 percent of sales of all oral liquid
22 formulations.

1 This graph shows the sale of oral liquid
2 formulations from year 2001 through year 2009. The
3 X-axis shows the years and the Y-axis shows the
4 number of eaches sold in millions. And as you can
5 see, the concentrated oral drops, represented by
6 the red line, was the most commonly sold oral
7 liquid formulation throughout the study period,
8 with a 66 percent increase in sales from year 2001
9 to year 2009.

10 This slide shows the sale of OTC single
11 ingredient acetaminophen products by strength.
12 Keep in mind that the sales of these strengths are
13 not specific to a particular formulation. For
14 example, the sale of the 80 milligram strength
15 included all doses, formulations, such as oral
16 drops, chewable tablets, and suppositories.

17 The percentage of sales by strength from
18 year 2001 to year 2009 was similar. During year
19 2009, the pediatric strength 160 milligram,
20 80 milligram, and the 120 milligram accounted for
21 approximately 30 percent of sales of OTC single
22 ingredient acetaminophen products. This amount

1 breaks down to 16 percent for the 160 milligram, 12
2 percent for the 80 milligram, and less than
3 1 percent for the 120 milligram.

4 I will now move on to describe the
5 prescription data for single ingredient
6 acetaminophen products. The SCI database was used
7 to obtain estimates of the number of outpatient
8 prescriptions dispensed for acetaminophen products
9 from year 2000 to year 2009.

10 The SCI database was a national level
11 projected prescription and patient-centric tracking
12 service which receives over 1.4 billion
13 prescription claims per year, representing over
14 120 million unique patients from a sample of
15 approximately 59,000 retail pharmacies in the U.S.

16 As shown in the previous slides, the vast
17 majority of acetaminophen products were sold as
18 over-the-counter. From here on, I will discuss
19 outpatient use of acetaminophen products captured
20 from prescription claims only, which represents a
21 small portion of the overall use of acetaminophen
22 products. Keep in mind that single ingredient

1 acetaminophen products provided in the next few
2 slides were OTC single ingredient products
3 dispensed under a physician order.

4 From year 2000 to year 2009, the number of
5 dispensed prescriptions for single ingredient
6 acetaminophen products decreased by 50 percent,
7 with 2.1 million prescriptions dispensed in year
8 2009. Concentrated oral drops formulation
9 accounted for around 5 percent of the total number
10 of dispensed prescriptions for single ingredient
11 acetaminophen products.

12 This graph shows the number of dispensed
13 prescriptions for single ingredient acetaminophen
14 products by dosage form. The X-axis shows the
15 years, and the Y-axis shows the number of dispensed
16 prescriptions in thousands.

17 As shown by the red line in the graph, there
18 was an 86 percent decrease in the number of
19 dispensed prescriptions for concentrated oral drops
20 formulation from 697,000 prescriptions dispensed in
21 year 2000 to 97,000 prescriptions dispensed in year
22 2009.

1 This table shows the percentage of single
2 ingredient acetaminophen products dispensed by
3 strength. Similar to the sales data, the
4 prescription market of these strengths are not
5 specific to a particular formulation. The
6 percentage of dispensed prescriptions by strength
7 from year 2000 to year 2009 were similar. In year
8 2009, the most commonly dispensed strength of
9 prescription single ingredient acetaminophen
10 products was 160 milligram, with 41 percent. The
11 80 milligram and 120 milligram strengths accounted
12 for around 3 percent and 2 percent, respectively.

13 I will now discuss the limitations of the
14 databases used to obtain these results. The IMF
15 database only captures approximately 50 percent of
16 all over-the-counter sales. These data do not
17 provide a direct estimate of patient use, but do
18 provide a national estimate of units sold from the
19 manufacturer to various channels of distribution.
20 We are unable to determine user numbers or
21 demographics, frequency of amount of over-the-
22 counter products purchased, or use at the consumer

1 level and concurrent product use.

2 The SCI database only prescribes outpatient
3 prescriptions used and capture products only at
4 prescription claims, which represent a small
5 portion of the overall use of acetaminophen
6 products. Over-the-counter product sales are not
7 captured.

8 To summarize, the sales of OTC single
9 ingredient acetaminophen products increased by
10 35 percent, with 151 million bottles or packets
11 sold in year 2009. The concentrated oral drops
12 formulation was the most commonly sold, oral liquid
13 formulation for OTC single ingredient acetaminophen
14 products.

15 The sale of the concentrated oral drops
16 increased by 66 percent from year 2001 to year
17 2009. The OTC single ingredient acetaminophen
18 product strengths most likely to be used in
19 pediatrics accounted for almost a third of the
20 total sales of OTC single ingredient acetaminophen
21 products.

22 Thank you.

1 DR. NEILL: So we'll now continue with the
2 FDA presentation by Dr. Pham -- I beg your pardon.
3 Dr. Goulding?

4 **FDA Presentation - Margie Goulding**

5 DR. GOULDING: Good morning. My name is
6 Margie Goulding, and I'm from the Division of
7 Epidemiology II. Can everybody hear me okay?

8 This presentation is on acetaminophen
9 exposure associated problems in children in the
10 U.S. It's a review of U.S. Poison Control Center
11 calls data for the years 2002 to 2008. This
12 analysis was only recently completed, so I
13 apologize, but it was not included in the FDA's
14 background package. This presentation will cover a
15 discussion of the study's objectives, the data
16 source and our outcome variables, the results, the
17 study's limitations, and our key findings.

18 The study objectives were to measure the
19 magnitude of the problem associated with exposure
20 or overexposure to acetaminophen in children,
21 particularly in those under 2 years old. We tried
22 to measure the magnitude of the problem at three

1 levels: broadly, in terms of calls to poison
2 centers; second, more narrowly counting only calls
3 that met our stringent criteria for overdose; and,
4 third, measures of problems or outcomes associated
5 with acetaminophen exposure and overexposure. An
6 additional study objective was to evaluate changes
7 in these measures in recent years using data for
8 years 2002 to 2008.

9 Next, I'm going to describe the data source
10 used for this analysis. The American Association
11 of Poison Control Centers, or AAPCC, maintains a
12 national database of information logged by the
13 country's poison centers, serving the whole U.S.
14 population, in all 50 states, Puerto Rico, and DC.
15 It is called the National Poison Data System, or
16 NPDS.

17 In 2008, the NPDS added almost two and a
18 half million human exposure calls or cases; I use
19 the terms interchangeably. That's up from 251,000
20 calls in 1983.

21 The AAPCC expects their coverage of calls to
22 poison centers is national since they put in place

1 the 1-800-222-1222 number around the year 2000.
2 Through this number, all incoming calls are routed
3 to a poison center or PC. So PCs and, in turn, the
4 NPDS, capture all the calls to the 1-800. So
5 anyone in the U.S. with access to a phone has
6 access to a poison center free of charge, 24/7, all
7 year, and these PCs are managed and staffed by
8 health care professionals with toxicology training.

9 People call poison centers for information,
10 as well as for advice after an exposure to a
11 potentially toxic substance. For this analysis, we
12 evaluated only exposure calls, not informational
13 calls. However, I should make it clear that not
14 all exposure calls received are necessarily a
15 poisoning or overdose. It could be the person just
16 gave or took a slightly excessive dose or a second
17 dose too soon after first dose, but not enough to
18 cause adverse effects or that it would meet our
19 stringent criteria for overdose, which I will
20 describe later.

21 In brief, poison center calls coverage is
22 believed to be national, but drug exposure and

1 drug-related problems are likely underestimated,
2 and drug-related deaths may be under-captured as
3 well in the NPDS.

4 Our analytic approach is a descriptive
5 analysis with a mix of examining counts of calls
6 data and using population-based rates to compare
7 call rates across age subgroups and over time. To
8 compare call counts in different size population
9 groups, we basically standardize by creating
10 population-based rates. We use the call counts as
11 the numerators, but for denominators, we don't have
12 good acetaminophen exposure estimates by year and
13 age group. So as a proxy, probably a poor one, but
14 the best we have, we used Census Bureau population
15 estimates as our denominators.

16 Our definitions. These are some of the
17 measures we created for the analysis. First, our
18 definition of overdose. Our definition of overdose
19 was met if any of these three criteria were met:
20 first, a 10-fold dosing error reported in the call
21 record; second, a dose greater than five times
22 Kaiser's recommended acetaminophen dose for

1 children by age; and, third, a dose greater than
2 the AAPCC's guidelines for emergency department
3 referral with acetaminophen exposure by age,
4 weight, and exposure duration, as shown in the
5 slide.

6 Using these three criteria allowed us to
7 avoid not being able to make an overdose
8 determination when the patient's weight information
9 was missing. But there were still cases,
10 approximately 10 percent, where the dose quantity
11 was missing and these calls ended up coded as not
12 overdose.

13 We also created a binary variable for severe
14 medical outcomes, which captured cases with signs
15 or symptoms that were categorized in the NPDS as a
16 major effect or a moderate effect. A major effect
17 involved life-threatening effects or effects
18 resulting in significant disability or
19 disfigurement, and we included deaths as a severe
20 medical outcome.

21 Three more binary outcome variables were
22 defined. The first was hepatic-related

1 abnormality, as indicated by meeting any of these
2 five clinical or lab value criteria shown on the
3 slide. The second was health care facility use.
4 The third was the case having been either
5 recommended or administered either of two overdose
6 therapies, either activated charcoal or
7 N-acetylcysteine, or NAC for short.

8 In this analysis, we examined poison center
9 calls for single substance acetaminophen alone
10 exposure calls in children 0 to 17 years old.
11 There were 265,558 such calls over the 2002 to 2008
12 period. For under 2-year-olds, the calls count was
13 approximately 42,000 or about a quarter of these
14 calls.

15 First, in our analysis, we looked at the
16 reason for the exposure call. The reason
17 categories with large counts were, one,
18 unintentional general; two, therapeutic errors;
19 and, three, intentional exposure with a suspected
20 suicidal intent.

21 For unintentional general, there were
22 approximately 172,000 cases or 65 percent of the

1 full call set. Unintentional general is where the
2 unsupervised child ingestions are coded. We looked
3 that the distribution of these cases by age.
4 Ninety-four percent of the 172,000 were in children
5 under age 6, mostly in 1 to 3-year-olds. And then
6 we confirmed our suspicions with NPDS managers at
7 the AAPCC, who agree that the unintentional general
8 reason category is a good proxy for unsupervised
9 ingestions by young children.

10 The second largest category was therapeutic
11 errors. These were calls about cases where the
12 caregiver or user made an error when trying to give
13 or take the medication. There were approximately
14 62,000 such cases or almost 24 percent of the full
15 call set.

16 The third largest category was exposures
17 deemed intentional with suspected suicidal intent.
18 There were approximately 23,400 such cases or
19 almost 9 percent of the full call set.

20 There were two categories with medium to
21 small counts that were of interest. Those were
22 intentional misuse and abuse, with 1.3 percent of

1 the full call set, and adverse drug reactions, with
2 0.3 percent of the full call set.

3 Given these reasons, we created two analytic
4 groups from the call data. Most of the cases from
5 the 265,558 were put into these two analytical
6 groups. Into the first group we put all the cases
7 where the exposure was believed to be due to an
8 unsupervised ingestion by a child under 6 years
9 old. Into this group we also put the cases for
10 kids ages 11 to 17 with suspected suicidal intent
11 or intentional misuse or abuse. We call all these
12 approximately 187,000 cases the unsupervised kids
13 cases and group them together, since they all
14 involve improper use of the medication.

15 While these cases, 23 percent of which were
16 under 2-year-olds, are important in that they can
17 cause harm and are a burdened on society and our
18 medical system, they don't really provide evidence
19 of an unsafe drug, just of misuse of a drug. So we
20 separated out these cases in our analysis.

21 A second analytic group we created includes
22 the therapeutic errors cases and the adverse drug

1 reaction cases. Together, we call these
2 approximately 63,000 cases the therapeutic mishap
3 cases group.

4 Unsupervised toddler ingestions of
5 acetaminophen is a known problem, as are the
6 suicide attempts in teenagers, and these problems
7 are clearly manifest in these data. But for the
8 purposes of the questions before this advisory
9 committee, I'm going to focus my discussion more on
10 the results in the group that includes therapeutic
11 errors in kids and not on all child age subgroups,
12 but primarily on the under 2-year-olds. In the
13 almost 62,000 therapeutic error cases, 32,580, or
14 approximately 53 percent, were in children under 2
15 years old.

16 Now, we're going to start with some more
17 results. The data in this table are static
18 measures of acetaminophen exposure associated
19 problems. They are counts for one time period, the
20 years 2002 to 2008 combined.

21 In this table, going across, we have the
22 three case groups, group one, two and three, as

1 previously described. Down the left side of the
2 table we have our outcome measure, overdose, using
3 our stringent criteria. The percentages based on
4 call counts are shown, but most of the counts are
5 not shown, and the denominators are shown under the
6 group titles.

7 In group 3, the therapeutic mishap cases
8 group, most of the cases involved dosing errors,
9 but they were not such extreme or egregious errors
10 such that only 6.1 percent of these cases qualified
11 under our strict overdose criteria, and the
12 overdose percentage was lower, 0.8 percent, in the
13 under 2-year-old age subgroup. And as we see in
14 the table, these percentages increased with the
15 users' age.

16 This pattern was also evident for the other
17 two groups, shown in the next two columns. In
18 general, the overdose percentages increased with
19 age. Not surprisingly, the group containing the
20 suspected suicide intent and intentional abuse and
21 misuse cases, that is, group 2, had higher overdose
22 percentages overall and in all of the age

1 subgroups.

2 This table has a similar setup as the last
3 one, but the outcome variables shown in the left-
4 most column are hepatic-related abnormalities,
5 severe medical outcome, and deaths, with both the
6 counts and percentages shown.

7 The therapeutic mishaps case group, group 3,
8 had 0.2 percent -- 2.3 percent of its cases with
9 hepatic-related abnormality and 0.33 percent with a
10 severe medical outcome, which is in line with the
11 relatively low or 6.1 percent overdose rate found
12 for group 3.

13 In group 2, the unsupervised kids cases
14 group, which includes the suspected suicide, abuse,
15 misuse cases, not surprisingly had higher
16 percentages than the other two groups on the
17 hepatic-related abnormality and severe medical
18 outcomes measures. But the percentage wasn't
19 higher on deaths, but this is probably because
20 there were very low numbers of deaths for all three
21 case groups. And for under 2 year olds, the deaths
22 counts were 5, zero and 3 for groups 1, and 3,
23 respectively.

1 For all three groups, the differences
2 between the hepatic-related abnormality counts and
3 the death counts may point to effective
4 intervention by health care providers.

5 In this table, we show health care resource
6 use outcomes in the left-hand column. On these
7 health care resource use outcome measures, again,
8 we see higher percentages for group 2 than for
9 groups 1 or 3. In group 3, therapeutic mishaps
10 cases, we see a low percentage, less than 4 percent
11 of these cases, receiving care at a health care
12 facility and an even lower percentage, less than 1
13 percent, being recommended or receiving activated
14 charcoal or NAC therapy. Thus, the health care
15 abuse burden from therapeutic mishaps involving
16 acetaminophen in kids appears to be relatively low.

17 In this table, we show the population-based
18 rates described earlier. The rates are counts per
19 one million population in that age group in that
20 year. And this table shows, for the full case set,
21 the population-based rates of overdose meeting our
22 stringent criteria appear to have increased

1 29 percent for the zero to 17-year-old age group
2 and 60 percent for the under 2-year-olds age group.

3 Please note this is the full case set, so it
4 includes a majority of cases that were unsupervised
5 ingestions in toddlers or young children, as well
6 as a substantial share that were suspected suicide,
7 abuse or misuse cases in teenagers. Also note that
8 these population-based overdose rates could look
9 lower if we excluded the approximately 28 percent
10 of the cases that had the maximum possible reported
11 as the dose quantity.

12 For therapeutic mishaps cases, in the
13 therapeutic mishaps cases group, on overdose, the
14 rates appear to have increased 27 percent for zero
15 to 17-year-olds and 37 percent for under 2-year-
16 olds over the 2002 to 2008 period. And on the
17 other outcome measures, HRR, SMO and health care
18 facility use, the rates were all relatively low to
19 begin with in 2002, but all appear to have
20 increased for both the zero to 17-year-old and
21 under 2-year-old age groups.

22 Primarily as a check on the data,

1 statistical correlations were calculated to make
2 sure the data and the outcome variables we created
3 were acting in the ways we expected. And we found
4 that the cases with an overdose determination in
5 both our unsupervised kids and therapeutic mishaps
6 analytic groups were positively and significantly
7 correlated with most of our outcome measures.
8 However, for both groups, overdose did not
9 correlate with death, probably due to the small
10 numbers. And the small death counts may be
11 primarily because of effective intervention, such
12 that the vast majority of overexposed persons
13 didn't die.

14 In the NPDS data, up to four scenario codes
15 per case are coded in therapeutic error cases. And
16 the top four therapeutic errors were inadvertently
17 giving or taking the medication twice; giving or
18 taking doses too close together; giving an
19 incorrect formulation or concentration; and,
20 dispensing cup or device errors. Forty-five
21 percent of these therapeutic error cases either had
22 taken or been given the medication twice or got the

1 doses too close together.

2 Limitations. There are several limitations
3 to this analysis, due primarily to the nature of
4 the data. First, calls to poison centers are
5 voluntary, so we expect under-ascertainment. NPDS
6 does not capture all drug exposures or all drug
7 exposure associated problems. Calling is voluntary
8 and not all people, even with access to a phone,
9 are willing or able to call. A person could be too
10 sick or incapacitated to call or serious about
11 committing suicide and not interested in getting
12 help, or they could be rushing to get to an
13 emergency department and not take the time to call
14 a poison center.

15 According to the AAPCC, 15 percent of NPDS
16 calls come from health care facilities, but the
17 rate of calling from EDs is very variable. An ED
18 may or may not call a drug overdose case into a PC.

19 In addition, calls are less likely from
20 exposed persons not experiencing adverse effects.
21 A 2004 IOM report estimated that the total number
22 of exposures reported to poison centers are

1 probably underreported by at least half and, as
2 already discussed, there's a low number of deaths
3 reported at NPDS, probably due to a mix of self-
4 selection, effective intervention, and a narrow
5 time window for information capture in the NPS
6 data.

7 In brief, the main strengths of the NPDS are
8 there's a large of calls from all over the U.S.
9 over a long period of time, but there's likely
10 underestimation of full number of exposed cases;
11 and also there is imprecise dosage information in
12 the majority of the call records. And as I've
13 already said, the inclusion of cases with a maximum
14 possible dosage reported could have inflated the
15 population-based overdose rates.

16 Lastly, we did not do statistical trend
17 tests on the call rates, because, one, we don't
18 know how much the calls count numerator really
19 captures the true universe of people with
20 acetaminophen exposure associated problems, and we
21 expect some under-ascertainment; and, two, we're
22 not really using correct denominators, which would

1 be only acetaminophen exposed persons. So we just
2 report the appearance of changes in the population-
3 based rates, but didn't do any statistical tests.

4 Key findings. Our first key finding is that
5 acetaminophen exposure in kids is still generating
6 problems, with about 32,000 to 46,000 poison center
7 calls a year and approximately 25 percent of those
8 in under 2-year-olds. However, we may not have a
9 correct estimate of the magnitude of the problem
10 from these call counts because the extent of
11 underreporting is unknown. But from what we did
12 see, the vast majority of these calls or cases are
13 for unsupervised ingestions in under 6-year-olds or
14 intentional suicide, abuse, misuse by teenagers.
15 So a lot of these cases should be preventable.

16 Our second key finding is that acetaminophen
17 exposure or overexposure problems in kids, on most
18 of our measures and in most of the age subgroups,
19 including the under 2-year-olds, appear to have
20 increased over the 2002 to 2008 period.

21 Unfortunately, even if we assume that we had
22 good estimates in these call numbers, we would want

1 to know how does the apparent 44 percent increase
2 in call counts from 32,000 in the year 2002 to
3 almost 46,000 in the year 2008 compare with any
4 change in persons exposed to acetaminophen.

5 Unfortunately, we don't have good
6 information on the number of persons exposed to
7 acetaminophen. So even creating population-based
8 rates, which helped us look at our measures across
9 age groups, didn't really allow us to evaluate the
10 trend over time, at least not statistically.

11 On this point, the AAPCC, in its 2008 NPDS
12 annual report, states, "These calls do not directly
13 identify a trend in the overall incidence of
14 poisonings in the U.S. because the percentage of
15 actual exposures and poisonings reported to PCs is
16 unknown."

17 Our third key finding is that acetaminophen
18 therapeutic error calls in kids were approximately
19 9 percent a year over the 2002 to 2008 period, with
20 about 53 percent of these in under 2-year-olds.
21 And 45 percent of these therapeutic errors in kids
22 were from accidentally giving the medication twice

1 or giving the doses too close together.

2 Thank you.

3 **Clarifying Questions**

4 DR. NEILL: Thank you. So we have a brief
5 period of time for clarifying questions. As you're
6 considering those, please note that we have four
7 presentations coming up that deal with both
8 hospitalization rates for children related to
9 acetaminophen toxicity and also the Adverse Event
10 Reporting System data later. So we'll try and
11 focus our questions on the two presentations that
12 we just heard.

13 Dr. Farber? Again, a reminder, please state
14 your name before your question.

15 DR. FARBER: Neil Farber. Two questions,
16 one for Dr. Pham and one for Dr. Goulding, both
17 regarding demographics.

18 Dr. Pham, I note that you didn't have any
19 ability to have demographics on your data. But I
20 was wondering, in terms of the prescription drugs,
21 do you have any information regarding insurance
22 providers? And second, for Dr. Pham, do you have

1 any demographics on the number on the overdoses in
2 terms of either anything about insurance or
3 socioeconomic status or anything like that?

4 DR. PHAM: This is Tracy Pham. Regarding
5 about the first question, for the prescription by
6 age, we did not look at that, but that could be
7 obtained from our database for the single
8 ingredient acetaminophen products. I'm sorry. We
9 don't have that data available, because we didn't
10 look at it for the review.

11 Regarding about the overdose incidence --

12 DR. FARBER: No. The second question is for
13 Dr. Goulding regarding any information about
14 demographics on the overdose kids.

15 DR. GOULDING: We have age distribution, but
16 health insurance, SES, no. That's not in the NPDS.

17 DR. NEILL: Dr. Santana?

18 DR. SANTANA: This is a question for
19 Dr. Goulding. When you looked at the poison
20 control data over this period of time, can you tell
21 us if there was an increase in other categories of
22 other medications that were not specifically

1 acetaminophen? I'm trying to normalize the data,
2 whether what we're seeing with this data is just
3 that these poison control centers are becoming more
4 publicly known and people are calling for many
5 other reasons, not necessarily just acetaminophen.

6 So can you give us an idea of this issue
7 with the acetaminophen, how much it occupies the
8 poison control data center issues?

9 DR. GOULDING: I didn't have access to other
10 unit level data, only acetaminophen files. So I
11 couldn't look at calls by particular drug. But if
12 you look at, overall, the calls in the annual
13 report, you see that -- I think I reported in '83
14 that they had 251,000 exposure calls and then in
15 2008, they had 2.5 million, so a 10-fold increase.
16 So, generally, the call volume is increasing, both
17 informational and exposure calls to poison control
18 centers.

19 DR. NEILL: Dr. Wright?

20 DR. WRIGHT: This question is for
21 Dr. Goulding. I was curious about the -- you
22 mentioned the strict criteria for overdose, I think

1 it was your slide number 9. And can you just -- in
2 characterizing the criteria for entry onto this
3 slide here, is it the same as the definitions that
4 you described earlier from the AAPCC?

5 DR. GOULDING: It's a combination of the
6 three. Let me go to that slide.

7 So this is our definition of overdose; if
8 they met any of these three, so report of a 10-fold
9 dosing error or exposure at five times Kaiser's
10 recommended dosing for children by age or the AAPCC
11 guidelines.

12 The problem with AAPCC -- these are the most
13 specific, the AAPCC guidelines, and they have by
14 age and by weight and by dosing duration, exposure
15 duration. But because they required weight and a
16 lot of the case report data didn't have a weight,
17 there was something like 20-30 percent. We
18 couldn't get an overdose determination because we
19 didn't have the weight. So that's why we filled in
20 with these other two.

21 So, basically, the Kaiser recommended dosing
22 levels, just what anyone gets when they go to their

1 pediatrician, it's the same, I think, Temple-based
2 age and weight, but we just used the age guidelines
3 for acetaminophen dosing for the kids.

4 DR. WRIGHT: Right. That's what I
5 suspected, because certainly in the experience in
6 the emergency department, that category there of
7 number 3, where you have incorrect dosing over a
8 period of time, not the acute, but the more chronic
9 exposure, is certainly a category of major
10 experience. And you're correct that that doesn't
11 often get reported, but I suspect that when you
12 looked at the number of children less than 2 in
13 that group 3 on slide number 9, I really suspect
14 that that's a major undercount there, because
15 that's the group of young children whose parents
16 are confused about the dosing, who bring them in at
17 some point well into the illness when they discover
18 that they've been getting a dosing that is
19 inappropriate.

20 Thank you.

21 DR. GOULDING: I don't know what you see in
22 the EDs, but I know from looking at another dataset

1 that picks up ED visits, the NEISS-CADES data, when
2 I looked at those for medical errors, I think there
3 was one or two, maybe just one case out of about 40
4 where there was that kind of repeated error, where
5 the parents kept giving the wrong dose over and
6 over, over an extended time period.

7 Also, in the NPDS calls, it was also a small
8 share, a minority, where there's a long-term
9 repeated problem exposure. Most of the calls, the
10 vast majority, were just an acute exposure case.

11 DR. NEILL: Dr. Notterman?

12 DR. NOTTERMAN: My question is actually the
13 same as Dr. Santana's, but I want to make sure that
14 I understood the answer that Dr. Goulding provided.

15 So we don't have information available, for
16 this setting at least, on the incidence of poison
17 center calls, hospitalizations, or serious adverse
18 events related to overdose for, for example, an
19 agent, single agent such as ibuprofen in
20 comparison, because knowing that would help frame
21 the conversation and the comparison.

22 DR. GOULDING: NPDS has it. I just don't

1 have it. We basically have a contract to get
2 certain unit level data from NPDS, from AAPCC, and
3 what we obtained were the acetaminophen data.

4 DR. NOTTERMAN: Thank you.

5 DR. NEILL: Dr. Reidenberg?

6 DR. REIDENBERG: A question for
7 Dr. Goulding. Your definition of severe medical
8 outcome included many events that would be
9 unrelated to acetaminophen. Do you know how many
10 or what fraction of these severe medical outcomes
11 were definitely due to the acetaminophen versus
12 other things that the patient could have been
13 taking concurrently?

14 DR. GOULDING: Well, one of the nice things
15 in the NPDS data is for every clinical effect, they
16 have a variable called relatedness, and that says
17 whether the effect is believed to be related to the
18 exposure, and we only took things where it said it
19 was related.

20 DR. NEILL: Dr. Goldstein?

21 DR. GOLDSTEIN: I just wanted to address
22 Dr. Notterman's and Dr. Santana's concerns. I just

1 looked at the 2009 report from NPDS online, and
2 acetaminophen seems to be -- just in terms of the
3 treatment given, NAC, seems to be one of the top
4 five in relation to any other drug toxicities.

5 DR. NEILL: Is that data something that
6 could be given to staff for distribution to the
7 committee maybe by tomorrow?

8 DR. GOLDSTEIN: I'd be happy to e-mail it
9 to -- who should I e-mail it to?

10 [No response.]

11 DR. GOULDING: The only thing I would
12 caution is when you look at that, they're talking
13 about all acetaminophen. So they're talking about
14 combination products to adults. It's the whole
15 universe of acetaminophen. As we know, a lot of
16 products have a little acetaminophen in them.

17 What we did in our analysis was --

18 DR. GOLDSTEIN: I would just point out that
19 people aren't going to treat a little acetaminophen
20 with N-acetylcysteine. So this would be for -- I
21 think you could safely infer that this would be for
22 true acetaminophen toxicity.

1 MR. NEILL: Dr. Curry? Then we're going to
2 come back to Dr. Parker and Dr. Farber.

3 DR. GOLDSTEIN: Excuse me. I'm sorry. It
4 is also broken down by age, as somebody was
5 mumbling that behind me.

6 DR. CURRY: As a toxicologist, I'd just like
7 to point out that it's extremely common to give
8 N-acetylcysteine intravenously when we do not have
9 any evidenced of acetaminophen toxicity. So
10 patients will come in and the history is variable.
11 You don't know the last time they took it.

12 With chronic ingestions, levels don't mean
13 anything. So the fact that N-acetylcysteine is
14 given cannot, in and of itself, be used as a
15 surrogate that acetaminophen toxicity was present.

16 DR. NEILL: Dr. Parker?

17 DR. PARKER: Dr. Goulding, maybe you can
18 clarify. I understand that the analysis was
19 limited to the single ingredient only. I assume
20 that's because when the calls come in, there's a
21 lot of clarification that goes on that it's not a
22 combination product.

1 Since we're looking at acetaminophen
2 generally, do you have or is there access to the
3 data on the toxicities -- to the calls that related
4 to too much use in the combination product that
5 contained acetaminophen?

6 DR. GOULDING: We have that data. I just
7 did not analyze it, because we wanted to make sure
8 that what effects we were seeing we could assume
9 basically came from the acetaminophen. We took
10 cases that the only substance that was reported for
11 the exposure was acetaminophen. So if they had any
12 other substance, that case was thrown out, that
13 case was excluded. And luckily --

14 DR. PARKER: I mean, could you tell us,
15 broadly, if there are more that come from
16 combination products or from single ingredient
17 calls?

18 DR. GOULDING: More toxicity or more what?

19 DR. PARKER: I'm sorry?

20 DR. GOULDING: When we looked at children
21 with an acetaminophen single active ingredient
22 exposure, there were something like 312,000 cases

1 where they also got another substance, and it could
2 be anything. But when we cut out those 15 percent,
3 we got down to 265,000, because in kids it seems
4 that, generally, parents are treating one issue,
5 fever or earache or something. So they're giving
6 one single ingredient product, largely, whereas we
7 know with adults, they tend to have a lot of
8 chronic conditions, so they have a lot of
9 combination products, multiple substances. But
10 with kids, you can drop the multiple
11 exposure -- multiple substance cases and still have
12 a majority with a single substance.

13 DR. PARKER: I'm not sure there's data to
14 support that people understand what they're buying
15 and taking, but okay.

16 DR. GOULDING: Well, whether they understand
17 it or not, I'm just telling you what was in the
18 calls. Only 15 percent of those 312,000 calls had
19 a second substance. A majority had single
20 substance, and that single substance was the
21 acetaminophen only, single active ingredient was
22 acetaminophen.

1 DR. PARKER: Great.

2 So I had a different question for Dr. Pham,
3 and that was just if you could -- in the summary
4 slide, slide 16, concentrated oral drop
5 formulations was the most commonly sold oral liquid
6 formulation for OTC single ingredient acetaminophen
7 products, and that goes along with the slide 6 that
8 showed the rate of rise with the oral drop
9 concentrated liquid formulation.

10 I wondered if you could put that next to the
11 timeline of FDA's work about dosing the
12 concentrated formulation for children under 2, the
13 rate of rise going up in sales.

14 Am I missing something there? The
15 concentrated formulation sold more after the work
16 to make that something that we weren't going to do.
17 Am I missing something here? If somebody can just
18 clarify that for me.

19 DR. HERTZ: Are you referring to going to
20 one single oral --

21 DR. NEILL: State your name.

22 DR. HERTZ: Sorry. Sharon Hertz, FDA. Are

1 you referring to one single concentration oral
2 solution acetaminophen product?

3 DR. PARKER: I was talking about the use of
4 the product in children less than 2, in general,
5 and the availability of the product on the market
6 for children under 2.

7 DR. FURNESS: This is Scott Furness from
8 FDA. What's your question, Dr. Parker?

9 DR. PARKER: So if we go back to the
10 recommendations about using the concentrated
11 formulation over-the-counter in children, in
12 infants, and the timeline for when that occurred
13 and look at the increase in sales and the timing of
14 when the recommendations were made about the use of
15 the product by the FDA, I just wanted to put those
16 two together timeline-wise; the use of infant
17 formulations of acetaminophen products for
18 children --

19 DR. FURNESS: I mean, we haven't really -- I
20 can't speak to anything that we would have done
21 that would have impacted that, nothing from the AC.

22 DR. PARKER: Okay. I'll withdraw it.

1 DR. PHAM: I just want to make a comment
2 that our analysis is very descriptive, even though
3 we don't know the reason why there's a trend and
4 increase in the concentrated oral drops
5 formulation.

6 DR. NEILL: Dr. Farber?

7 DR. FARBER: Neil Farber. This is for
8 Dr. Goulding, almost more a comment than a question
9 or partly a question.

10 On your last slide, you indicated that
11 45 percent of the errors occurred because of giving
12 medication twice or doses too close together. For
13 the purposes of our discussion, one of the things
14 that struck me is that almost 14 percent or
15 approximately 1,000 cases per year were due to
16 incorrect doses or dispensing cup/device errors.

17 I wondered if you might want to comment on
18 that.

19 DR. GOULDING: I just showed the top four,
20 but, yes, there were other problems; just giving
21 too much or there were problems with the wrong dose
22 being -- so wrong dose being administered and wrong

1 dose being given by the pharmacist. There were
2 various problems, but I just showed the top four.

3 I'm sorry. And there's another presentation
4 coming that will discuss medication errors with
5 some more detail.

6 DR. NEILL: Dr. Rosenthal?

7 DR. ROSENTHAL: Thank you. It's Jeff
8 Rosenthal. Two questions, and they may be related
9 to the some of the issues that Dr. Parker was
10 trying to drill down on.

11 The first I'll direct to Dr. Goulding. But
12 one of the areas of concern regarding the use of
13 over-the-counter combination medicines is that
14 there is the potential for children to receive an
15 excessive dose of acetaminophen if a care provider
16 gives a labeled dose of a combination medicine and
17 then a labeled dose of single agent acetaminophen.

18 How would an occurrence like that be
19 categorized, as an unintentional general or as an
20 unintentional therapeutic error, or would it not be
21 caught because we've eliminated any exposures to
22 combination medicines in the data that you've

1 presented?

2 DR. GOULDING: What pushed the dose over was
3 they gave concomitantly two forms of drugs with
4 acetaminophen, and that wouldn't be captured in the
5 analysis we did, because we threw out the multiple
6 substance exposures. We only kept the single
7 substance exposures.

8 So it would only be that it would be picked
9 up as a therapeutic error in those single substance
10 acetaminophen exposures if you gave an excessive
11 dose, or the dose too frequently, or you used the
12 wrong dosing device, or you gave the 10-fold dosing
13 error. There were 10 different kinds of errors
14 that were coded in the data.

15 DR. ROSENTHAL: Okay. Thank you. And then
16 one more quick question, and this is probably more
17 appropriately directed to Dr. Pham.

18 I, too, am curious about to what we should
19 attribute the rise in utilization or sales between
20 2001 and 2009 for an agent that's been around for
21 longer than I have. And so one of the questions
22 that popped into my mind was, I wonder when the

1 aspirin recommendations changed in kids and whether
2 there aren't other things going on in the over-the-
3 counter environment that are impacting or reflected
4 in the sales of acetaminophen.

5 I'm wondering if anyone has any insight into
6 some of those factors.

7 DR. PHAM: This is Tracy. I would love to
8 be able to have an answer for as of why the
9 concentrated oral drops had gone up since year
10 2001. But since our database is only descriptive,
11 as I said before, we don't have a reason. We don't
12 know. There could be many reasons as of why the
13 things that are happening in the market could cause
14 the increase in the concentrated oral drop
15 formulations.

16 DR. ROSENTHAL: So I'd be interested in any
17 other reflections around the table, even if they're
18 not specifically data-driven answers.

19 DR. NEILL: Dr. Kweder?

20 DR. KWEDER: I can provide some insight.
21 The pattern that you see for pediatrics is exactly
22 the same as you see for adults, and, basically,

1 it's kind of a question of -- it's a chicken-and-
2 egg question.

3 Basically, what we've concluded is that a
4 lot of this has to do with just the market. It is
5 a market. This is one of the most -- as an active
6 ingredient, acetaminophen is one of the most
7 commonly utilized active ingredients on the OTC
8 market, and the pattern of sales and
9 increase -- the curves for adults are the same as
10 the curves in children.

11 DR. NEILL: Dr. Cohen?

12 DR. KWEDER: And the aspirin decisions, the
13 changes in aspirin were from the 1980s.

14 DR. COHEN: This is more speculation than
15 fact, and I don't have any data to support it, but
16 my observation is that there are more manufacturers
17 of the acetaminophen products in the concentrated
18 drops, especially in recent years.

19 For example, we've seen -- and one of the
20 issues -- and I don't know where to talk about it
21 or exactly when, but one of the issues, and it's
22 kind of been touched on, I guess, in other

1 committees, is the issue of brand name extensions.

2 So what we're seeing is, for example, there
3 is a Triaminic now infant drops, but obviously
4 there are many other Triaminic products, and we've
5 had situations where patients would bring to the
6 counter both a Triaminic product and acetaminophen
7 drops as well.

8 DR. NEILL: I've got a question for Dr. Pham
9 that may relate. You used a unit which I've not
10 run across before, eaches from the IMS data, which
11 tells you how much time I spend in the IMS data.

12 How do eaches relate to -- and I understand
13 eaches to be a packet, bottle or vial in a unit,
14 whatever a unit is. How do those relate to doses,
15 and have there been year-over-year changes in how
16 doses relate to eaches?

17 DR. PHAM: No. For the IMF database, they
18 just measure the sales volume. So it doesn't
19 measure how much is being dosed for a patient since
20 we don't have any patient demographics.

21 DR. NEILL: The concern here being, of
22 course, that packaging changes, price

1 changes -- and I didn't -- you probably said
2 whether those were adjusted dollars. But the total
3 number of doses dispensed or used that might
4 influence calls to a poison center I think may be
5 distantly related to sales, if sales are described
6 as eaches. And those of you that know the data
7 better than I could probably comment on that.

8 But I'm hearing you say there's no direct
9 connection between doses and eaches. The unit
10 stays constant from IMS over time, although what
11 that unit measures may change.

12 DR. PHAM: Well, for eaches, basically, it
13 could be like 30 bottles of 500 tablets -- like 30
14 bottles of 500 tablets of 500 milligram.

15 DR. NEILL: I'm just wondering whether, for
16 example, the total volume of liquid concentrate,
17 80 milligram per .8, the total volume in a
18 dispensed each may have changed. It sounds like
19 across shelf-keeping units, that may be no
20 different over time.

21 DR. PHAM: Well, if we're looking at the
22 80 milligram per .8 ml, the eaches is describing

1 how many bottles of that 80 milligram per .8 ml
2 that were being packaged and sold.

3 I'm sorry. I'm not really sure if I'm
4 getting to your answer, to answer your question.

5 DR. NEILL: There may not be an answer. I'm
6 just trying to relate each to something which is,
7 to me, more meaningful. And I think to the
8 question at hand, which is we've got data now from
9 poison control centers, which is measured in calls,
10 but has been extrapolated into cases that
11 presumably relate to doses, but the data on sales
12 is being given to me in dollars and eaches. And I
13 just don't know how to relate them; that's all.

14 DR. MEHTA: I'm Hina Mehta, OSC, FDA.
15 Eaches here refers to, for example, an 80 milligram
16 per .8 ml concentration. Regardless if it comes in
17 a 5 ml bottle, 10 ml bottle, it's considered one.

18 Does that make sense? And each manufacturer
19 makes different amounts.

20 DR. NEILL: So that does make good sense to
21 me. And it then stands to reason that while sales
22 may change over time, how many doses may or may

1 not.

2 So without using my chair's prerogative to
3 continue to pummel you, we've got Drs. Griffin,
4 Watts, Rakowsky, and Farber.

5 Dr. Griffin?

6 DR. GRIFFIN: I'm Marie Griffin. I don't
7 know if anybody knows this answer about how
8 pediatricians prescribe acetaminophen or recommend
9 acetaminophen for when they give immunizations.
10 Has that changed over this last 10 years and kids
11 are getting a lot more shots or immunizations? I
12 don't know what the current recommendations are.

13 DR. RAKOWSKY: Alex Rakowsky. There was
14 some concern about an immune response being blunted
15 by the use of ibuprofen or acetaminophen with some
16 animal data from about three or four years ago,
17 which really didn't pan out clinically.

18 So I think the recommendation currently is
19 PRN. It's recommended to parents to give it for
20 pain or discomfort. It's not discouraged. There
21 probably was a block of about an eight-year period
22 where it was sort of discouraged, not to use it,

1 but I think that has sort of passed.

2 I think the majority of people in practice
3 will now encourage its use for PRN reasons.
4 There's not a standard dose to give before a
5 vaccine, but it's not uncommon to have a parent do
6 it.

7 DR. NEILL: I can certainly comment, in my
8 practice, part of the issue is exactly that
9 science, but also the joint commission requirements
10 for stocking and dosing and dispensing doses in the
11 office. So the logistics of that are such that we
12 no longer keep it in the office for that purpose
13 and don't do it as a matter of course.

14 Dr. Watts?

15 DR. WATTS: Again, just speculation, but one
16 of the things I've noticed in practice with
17 insurers is that insurers used to pay for these
18 over-the-counter medications if a physician wrote a
19 prescription for them. So many people would ask
20 for prescriptions specifically so their insurer
21 would pay for it.

22 That practice has pretty much died out over

1 the last 10 years. That may potentially be yet
2 another explanation for the increase.

3 DR. NEILL: And did you have a question,
4 Dr. Watts? Dr. Rakowsky, you had a question.

5 DR. RAKOWSKY: Similar to what Dr. Watts
6 just mentioned, there is also the use in -- and
7 Dr. Watts mentioned this as well. There is always
8 commonly the use of Tylenol or acetaminophen in
9 clinic or having families go home with small sort
10 of sample bottles of it.

11 Does the utilization data capture that
12 information in any way, shape or form? In other
13 words, in the past, parents would go home
14 potentially a two or three dose mini-bottle, which
15 isn't being done anymore. So is the increase in
16 prescriptions potentially due to that?

17 DR. NEILL: I don't know if any staff care
18 to address that.

19 DR. MEHTA: Hina Mehta. It only captures it
20 if it's sold to the physician's office. So these
21 normally are not sold. It's just a lot of times, I
22 guess, the physician gets a sample from the

1 manufacturer or company or whatever. So that would
2 not be captured.

3 DR. NEILL: So true to my experience with
4 most of these meetings, we have now used up any
5 time that we've saved and we're back on schedule.

6 [Laughter.]

7 DR. NEILL: I have approximately 11:04. So
8 why don't we proceed with a presentation from FDA.
9 Dr. Ahmad?

10 **FDA Presentation - Rizwanuddin Ahmad**

11 DR. AHMAD: Good morning. My name is Rizwan
12 Ahmad. And this morning I'll be talking about
13 hospitalization rates for acetaminophen associated
14 poisonings in children. This talk replaces the
15 counts of hospitalizations provided in the
16 background package from the SDI database.

17 We chose to provide data from the nationwide
18 inpatient sample instead since it is based on a
19 larger number of hospitals and also allows
20 calculation of population-based rates. Like the
21 previous presentation, this study was recently
22 completed and was not included in the background

1 package.

2 Here is an outline of my talk. I'll give
3 you the objective, the background methods, results,
4 limitations, summarize the key findings, and
5 acknowledge my collaborators at the Agency for
6 Health Care Research and Quality.

7 The objective of the study was to estimate
8 the rate of hospitalization due to acetaminophen
9 associated poisonings in children. The nationwide
10 inpatient sample is the largest all inpatient care
11 database in the U.S., containing data on nearly
12 eight million hospital stays per year from
13 approximately 1,000 hospitals.

14 NIS is from the family of health care cost
15 and utilization project sponsored by the Agency for
16 Health Care Research and Quality. NIS provides
17 national estimates. The sampling frame for NIS
18 data is discharge records from all hospitals in 44
19 states, which comprises 95 percent of all U.S.
20 discharges.

21 In the next few slides, I will very briefly
22 go over the methods. We extracted data and

1 analyzed it from NIS for 11 years, from 1998
2 through 2008. The unit of analysis is hospital
3 discharge. We use relevant ICD-9 codes to identify
4 cases with evidence of acetaminophen associated
5 poisoning from all listed diagnoses during
6 inpatient hospital stay. Please note that for this
7 analysis, we did not exclude potential poisoning
8 from other drugs.

9 In cases of acetaminophen associated
10 poisonings, we identified cases suggestive of
11 hepatotoxicity, with all these relevant ICD-9
12 codes, as shown in this slide. Rates of
13 hospitalization per 100,000 use population were
14 estimated. The numerator was the number of
15 hospitalizations. The denominator was the U.S.
16 population in specified age groups as reported in
17 the U.S. Census in July of each year.

18 Data were analyzed using SAS and SUDAAN.
19 Statistical significance across time was evaluated
20 by comparing confidence intervals in the earliest
21 time period, that is, 1998-1999, to that in
22 period 4, 2006-2008.

1 In the next few slides, I will present the
2 mean results of the study. This table shows the
3 rates of acetaminophen associated poisoning
4 discharges by age. Overall, there is a significant
5 increase in the rate of acetaminophen associated
6 poisoning discharges in all ages, and it increased
7 from about 11 per 100,000 U.S. population in 1998-
8 1999 to 15 in 2006-2008. This is the first line,
9 which says "all ages." But in children less than 2
10 years, the red font, the overall rate of hospital
11 discharge for acetaminophen associated poisoning
12 declined from 2 to 1.6.

13 In children 2 to 12 years of age, the blue
14 font, the overall rate of hospital discharge for
15 acetaminophen associated poisonings increased from
16 1.19 to 1.35 in this study period.

17 This table shows the rates of acetaminophen
18 associated poisoning discharges with hepatotoxicity
19 per 100,000 U.S. population by age. I will
20 concentrate only on children less than 2 years of
21 age, the red font. In children less than 2 years
22 of age with acetaminophen associated poisoning and

1 hepatotoxicity, there was about 50 percent decline
2 in the rate of hospitalization from .300 per
3 100,000 U.S. population in 1998-1999 to .146 per
4 100,000 U.S. population in 2006-2008.

5 Incidentally, there was no change in acetaminophen
6 associated hepatotoxicity in other pediatric age
7 groups.

8 This slide shows the inpatient mortality in
9 children with acetaminophen associated poisonings.
10 Inpatient mortality is based on a discharge status
11 of death in hospital. Overall, there were 63
12 deaths in children less than 18 years of age who
13 were hospitalized with a diagnosis code of
14 acetaminophen poisoning. As mentioned previously,
15 we did not exclude other potential causes of
16 poisoning in the study. In this 11-year study
17 period, overall, there were a little under 77,000
18 hospitalizations in children less than 18 years of
19 age.

20 This slide lists some of the limitations of
21 the study. The unit of analysis is hospital
22 discharge, not patient, which means patients with

1 multiple hospitalizations with acetaminophen
2 associated poisoning could be counted multiple
3 times.

4 There is an underestimation of the total
5 estimated discharges since NIS excludes poisoning
6 treated in federal hospitals and in outpatient
7 settings. Medical records are not available to
8 validate diagnosis. Data are based on
9 administrative records that are used for billing
10 purposes and reimbursement, and clinical details
11 are limited to ICD-9 codes. In this study, we did
12 not exclude poisoning due to concomitant
13 medication.

14 Finally, the data do not provide information
15 on how the poisoning happened, whether it was
16 unsupervised ingestion or therapeutic errors.

17 The next speaker, Dr. Marie Suarez-Almazor,
18 has abstracted charts from the pediatric emergency
19 department visits for acetaminophen associated
20 poisonings and will share some of her findings in
21 how these poisonings might have happened.

22 To summarize the key findings of the study,

1 the rates of hospitalization across all ages
2 increased from about 11 per 100,000 U.S. population
3 in 1998-1999 to 15 in 2006-2008. However, in
4 children less than 2 years of age, the overall rate
5 of hospitalization has declined.

6 Hepatotoxicity with acetaminophen associated
7 poisoning has increased overall. There was no
8 significant change for children in the 2 to 12 or
9 13 to 17 years of age. Yet, we saw about a
10 50 percent decline in acetaminophen related
11 hepatotoxicity in children under 2 years of age.

12 Finally, I would like to acknowledge my
13 collaborators at the Agency for Health Care
14 Research and Quality, Dr. Anne Elixhauser and Janet
15 Pagan-Sutton, who is the contractor.

16 That concludes my presentation. Thank you.

17 DR. NEILL: Thank you.

18 Dr. Suarez-Almazor?

19 **FDA Presentation - Marie Suarez-Almazor**

20 DR. SUAREZ-ALMAZOR: Good morning. I'm
21 going to present the results of a small study that
22 we have conducted in Houston, Texas. This has been

1 sponsored by the Agency for Health Care Research
2 and Quality and the Food and Drug Administration.

3 The aims of our study were more qualitative
4 than some of the other presentations. The first
5 thing that we had was to qualitatively explore
6 knowledge, attitudes, beliefs, and practices
7 regarding parental administration of over-the-
8 counter acetaminophen to children. Our second aim
9 was to establish which circumstances, by chart
10 review, such as error or intentional overdose, led
11 to events of acetaminophen overdose in children
12 visiting the emergency room.

13 For the first aim, we did both focus groups
14 and in-depth interviews. We wanted to administer
15 both the administration of acetaminophen to
16 children and self-administration of acetaminophen.
17 We had different groups. We had parents of
18 children less than 8 years old, adults from two
19 different groups, and adolescents. For this
20 presentation, I'm mostly going to consternate in
21 parents of children.

22 The setting was in Houston and we had

1 participants from two different clinics; first, a
2 private, outpatient clinic, the Kelsey-Seybold
3 Clinic, which is the largest outpatient system in
4 Houston; and, the second one, a public county
5 hospital within the Harris County Hospital
6 District, called the People's Clinic.

7 These are the participant characteristics.
8 For the parents of children, we had three groups,
9 one from Kelsey, the private setting, and two from
10 the People's Clinic. So I'm just going to
11 summarize the data on the right column, which is
12 the total number of participants.

13 We had 15 participants with a mean age of
14 35. Ninety-three percent of them were female, 40
15 percent were Hispanic, and 47 percent African-
16 American. Thirteen percent had completed high
17 school and the rest had some college or a
18 bachelor's or advanced degree.

19 Overall, we wanted to explore different
20 content areas. We wanted to know about the
21 knowledge of acetaminophen products, what were
22 their beliefs about benefits and risks, patterns

1 and frequency of use, where did they get the
2 information for use; also, if they had any related
3 experiences from peers that they could share with
4 us; and, finally, views about the labeling and the
5 clarity of the labeling, packaging, and, also,
6 legislation.

7 So the salient finding of the focus groups
8 was that, in general, parents had very positive
9 views about the benefits of acetaminophen and they
10 felt it was an effective treatment for their
11 children.

12 In general, participants in the public
13 setting were more concerned about risks. In
14 general, they used it for fever, teething, and
15 after shots, and patients were proactive in trying
16 to obtain the medication, but they also said that
17 they had some concerns about labeling.

18 Overall, they said they would appreciate
19 larger and bolder print. They felt it was
20 important to highlight the most salient
21 information. They felt that the warnings should be
22 clearer and that the information should be

1 consistent. And they stated that they would like
2 to have a dropper or a cup in all preparations for
3 children.

4 Our second aim was to examine children
5 visits to the emergency room in Texas Children's
6 Hospital, the largest children's hospital in the
7 Houston area. So we examined medical records to
8 the ER from 2008 to 2010. We selected cases on the
9 basis of primary or secondary diagnosis with
10 predetermined ICD-9 codes.

11 We excluded those patients that had been
12 transferred from other settings. We also excluded
13 when the ingestion or suspicion of acetaminophen
14 was not confirmed in the chart, and, also, those
15 cases that reported adverse drug reactions but were
16 not clearly overdose or potential overdose. Again,
17 we wanted to qualitatively examine what were the
18 circumstances surrounding the overdose that led to
19 the visit to the ER.

20 We used a number of different codes. You
21 have this slide in your package. I'm just going to
22 say that code 965, which is listed number 5 here,

1 was the most sensitive code of all of the ones we
2 used. But, again, we were very comprehensive
3 because we wanted to have high sensitivity in the
4 ascertainment of cases.

5 So overall, with these codes, we identified
6 426 cases. Of these, we excluded several because
7 of our exclusion criteria that I mentioned before.
8 So, overall, there were 98 cases where we felt
9 there might have been an exposure to an overdose.
10 Of these, 23 were 2 years or less, and these are
11 the ones that I'm going to base the rest of my
12 presentation on.

13 Overall, there was one infant that was less
14 than 6 months old, one was between 6 and 1 year,
15 and 21 had between 1 year and 2 years of age. Half
16 were, roughly, males, and the race was white in
17 56 percent of the cases, Hispanic in 35 percent,
18 and black and Asian in 4 percent. As I mentioned
19 before, the codes with 965 were the most frequently
20 represented.

21 Not all patients had serum acetaminophen
22 levels performed, but of those who had it

1 performed, approximately 90 percent had levels
2 below 10 micrograms per milliliter. And liver
3 function tests were not performed in all, but as
4 you can see in this slide, for those who had them
5 performed, AST and ALT levels were either normal or
6 very mildly elevated. Only one patient had NAC
7 administration, and there were no serious events,
8 such as death or liver failure among these 23
9 patients.

10 We then examined the circumstances
11 surrounding the possible overdose. In all cases,
12 this was unintentional and, as you can see here, in
13 five cases, or 22 percent, it was an error in
14 dosing from the caregiver, most frequently a
15 parent.

16 Most frequently, again, tablets were the
17 medication form, 52 percent, with 4 percent, just
18 one, melt away. In general, the ingredient was
19 just a single ingredient preparation, and most of
20 the patients had a single acute ingestion, but
21 about 13 percent of them had multiple ingestions
22 over a period of two to three days. In some cases,

1 it was not stated the length of period for the
2 overdose.

3 This slide summarizes the five cases where
4 there was caregiver error. All of them were with a
5 liquid preparation. In three cases, it was clearly
6 stated in the chart that the caregiver had had
7 difficulty understanding the dosing.

8 The cases are one infant of 6 months who
9 received 30 milliliters of an unidentified
10 preparation over two days; an infant of 15 months
11 who received 500 milligrams in two hours for 41
12 milligrams per kilo dose; a 23-month child who
13 received three bottles over three days, which were
14 given whenever the baby cried, this infant was
15 administered NAC. In the other two cases, one 4-
16 month-old child received 16 milliliters over two
17 days, and a 23-month child had an error in dosing
18 for two days where he was given a children's dose
19 instead of an infant dose.

20 So in conclusion, in the qualitative study,
21 participants had concerns and had suggestions about
22 more clear labeling of acetaminophen products.

1 Twenty-two percent of the ER admissions were
2 examined were caused by errors in dosing by the
3 caregiver, and the caregivers had difficulty
4 understanding labeling, as per medical records.
5 Fortunately, no serious adverse outcomes were
6 observed in this cohort of children.

7 Thank you.

8 **Clarifying Questions**

9 DR. NEILL: Thank you, Dr. Suarez.

10 So we've got a brief period of time for
11 questions for Dr. Ahmad and Dr. Suarez. If you
12 could hold your hand up so that we can get them
13 out. Let's start with Dr. Santana, then Rakowsky,
14 then Farber, then Landis, then Notterman.

15 DR. SANTANA: For the last presenter, can
16 you give us a little bit more detail --

17 DR. NEILL: And please remember to state
18 your name.

19 DR. SANTANA: I'm sorry. Victor Santana.
20 For the last speaker, can you give us a little bit
21 more detail about the methodology of your focus
22 groups? Were these questions that you guys had

1 ahead of time presented? Was it free-floating?
2 Did you have case scenarios? Did you have labels?
3 I'm trying to understand a little bit more the
4 science of the methodology.

5 DR. SUAREZ-ALMAZOR: Yes. These were guided
6 focus groups. So we had a list of guiding
7 questions with probes. And we didn't use
8 scenarios, but we used different forms of packaging
9 and asked participants to comment on the packaging
10 and offer suggestions as to how they would improve
11 the packaging. We also asked them to tell us
12 stories about circumstances where they had had
13 problems or they knew of someone who may have had
14 problems with the administration of acetaminophen.

15 DR. SANTANA: I noticed that there was a
16 large proportion in your focus group of Hispanic
17 individuals.

18 DR. SUAREZ-ALMAZOR: Yes.

19 DR. SANTANA: So how did you do that? Did
20 you conduct those in English? Did you have Spanish
21 materials?

22 DR. SUAREZ-ALMAZOR: One of them was

1 conducted in Spanish, and a qualitative researcher
2 who did the analysis is bilingual. Houston has
3 40 percent of Hispanic origin population, but the
4 focus groups for this particular group had
5 two -- two of them were conducted with
6 patients -- well, the parents of patients from the
7 county clinics, and the county clinics have a very
8 high representation of Hispanic and African-
9 Americans. Almost 90 to 95 percent are ethnic
10 minorities. So two of the focus groups were from
11 those clinics. So that's why --

12 DR. SANTANA: I haven't picked up a bottle
13 of acetaminophen in a while. Is there a package in
14 Spanish? I'm not familiar.

15 DR. SUAREZ-ALMAZOR: I believe almost every
16 single -- maybe the FDA wants to comment, but I
17 think, in general, there's a translation in Spanish
18 in the packages.

19 Isn't it? In some of them? No?

20 DR. SANTANA: I don't think so, but I can be
21 corrected.

22 DR. NEILL: Dr. Rakowsky?

1 DR. RAKOWSKY: Thank you, Dr. Suarez, for
2 your presentation. Just a quick question about the
3 rationale for excluding the transferred patients.

4 DR. SUAREZ-ALMAZOR: Well, we excluded the
5 transferred patients mostly because we felt that we
6 would not have enough information about the
7 circumstances on how this had happened. This was
8 more qualitative in nature, to some degree, and
9 many of these patients were transferred. They were
10 admitted to the emergency room just to be possibly
11 admitted. But we might eventually look at those as
12 well. Our criteria was that we would just look at
13 the ones who came directly.

14 DR. NEILL: Dr. Farber?

15 DR. FARBER: This is Neil Farber.

16 Dr. Suarez, I note that in your findings
17 about the qualitative study, you say that there
18 were concerns about labeling. I was wondering if
19 you probed for and found any coding scheme about an
20 indication of actual lack of understanding of how
21 to administer acetaminophen.

22 DR. SUAREZ-ALMAZOR: Yes. In some cases,

1 the participants said they had difficulty
2 understanding what it really meant and how much
3 they had to give, what it really meant. Yes.

4 DR. NEILL: Dr. Landis?

5 DR. LANDIS: Yes. Wini Landis.

6 Again, Dr. Suarez, on your caregivers that
7 had difficulty understanding the dosing, did you do
8 any kind of correlation between the ethnicity, the
9 Hispanic group versus the non-Hispanic group? And
10 for clarification, the infant drops and
11 acetaminophen that you find in a pharmacy is not in
12 Spanish. There is an 800 number on most bottles,
13 but even if you call, a lot of those phone calls do
14 not give them access at that point of information
15 for someone who is Hispanic.

16 DR. SUAREZ-ALMAZOR: Well, in general, we
17 found -- and, again, we didn't divide the -- okay.
18 The Hispanic only, I can't recall exactly. What I
19 know is that the ones from the People's Clinics,
20 which were the public clinic patients, had more
21 difficulty understanding or expressed more
22 difficulty understanding, and also had more

1 concerns about safety.

2 DR. NEILL: Dr. Notterman?

3 DR. NOTTERMAN: This is for Dr. Ahmad or
4 even one of the speakers from the previous group of
5 presentations.

6 I wonder if there's any information on
7 stratifying patients who have come for toxicity or
8 overdose with respect to the type of formulation.
9 And by that, I mean between the concentrated drop,
10 100 milligrams per ml, or tablet size.

11 DR. AHMAD: In the nationwide inpatient
12 sample that we did the study, that is not something
13 we can study. And I think in the case of NPDS, we
14 can. We can distinguish what the different
15 formulations are. But for this project, we didn't
16 get that data.

17 DR. NEILL: I have Drs. Engle, Rogers, and
18 then Nelson. Dr. Engle?

19 DR. ENGLE: This question is for Dr. Suarez.
20 This morning I haven't heard much comment on dosing
21 errors that involve underdosing. And as a
22 pharmacist, we tend to see a lot of patients

1 underdosed when they come into the pharmacy. Kids
2 grow out of their doses. They may not read the
3 label correctly. The age may not match the weight.

4 So my question for you is, with aim
5 number 1, where you actually had those focus
6 groups, did you at all address with those parents
7 or caregivers how they dose the child in terms of
8 looking for issues with underdosing? Because our
9 poison data and all, you're not going to pick that
10 up when you're looking for adverse effects, but
11 it's still an issue with adverse effects in terms
12 of people wanting other drugs because they think
13 acetaminophen doesn't work, when, in reality,
14 they're not given enough.

15 So I'm just curious. Did you look at that
16 at all?

17 DR. SUAREZ-ALMAZOR: That's an important
18 point, but we didn't look at that. We didn't probe
19 at all for underdosing.

20 DR. NEILL: Dr. Rogers?

21 DR. MARTINEZ-ROGERS: Norma Martinez-Rogers.
22 Coming from Texas myself, 50 percent of our

1 Hispanics drop out of school, don't complete high
2 school. So I'm wondering, in terms of labeling,
3 that even if it's in English and they read some
4 English, they may not be able to read the level of
5 the label, because most Latinos read at third grade
6 level.

7 Secondly is that in your studies, when they
8 talked about labeling, were these mostly
9 English-speaking Hispanics that were talking about
10 labeling or were they talking about labeling also
11 in your bilingual group?

12 DR. SUAREZ-ALMAZOR: Everyone talked about
13 labeling because that was one of the questions that
14 we had, and we spent some time looking at the
15 packages. So everyone had some comments, in
16 general.

17 But it was the group in the People's Clinic,
18 which included the Hispanics, that felt a little
19 more uncomfortable with the understanding of the
20 labels. But everyone had comments about it.
21 Because of the way the focus group was run, we
22 placed the question to the group, then we'd probe,

1 and, in general, if there are participants that
2 haven't been very verbal, we asked them
3 specifically, "Do you have any comments about
4 this?" and, in general, everyone had some comments.

5 DR. MARTINEZ-ROGERS: So am I to assume then
6 that everybody was able to read that was in your
7 groups?

8 DR. SUAREZ-ALMAZOR: Yes.

9 DR. MARTINEZ-ROGERS: Interesting,
10 because -- just a small comment in that we had a
11 patient that the doctor said take a tablet once a
12 day, but the doctor told it to the wife. The wife
13 gives it to the husband, and the medicine is for
14 the husband. And "once" in Spanish is "once,"
15 which means 11. So he took 11 tablets. Just a
16 comment and FYI.

17 DR. NEILL: Dr. Nelson?

18 DR. NELSON: Ed Nelson. Could I ask what
19 label you used for the under 2? Because there is
20 no OTC label on an under 2 package? Did you derive
21 one from --

22 DR. SUAREZ-ALMAZOR: We didn't use under 2.

1 We had parents of children under 8.

2 DR. NELSON: Parents under 2 were never
3 surveyed in this group.

4 DR. SUAREZ-ALMAZOR: No. The under 2 is
5 what we used as a category for the emergency room.
6 Some of the parents who had under 8, I will have to
7 look at the data, may have had children who were at
8 the time 2 or under. But they all had to have
9 children that were under 8. So at one point, they
10 had children under 2, obviously.

11 DR. NELSON: So they didn't make up a dose
12 for under 2 children then.

13 DR. SUAREZ-ALMAZOR: No, no. We just showed
14 some of the labels and asked them questions about
15 it. "Is this clear to you?" "Do you understand
16 what it means?" "Do you know how much you would
17 have to give?" Those kinds of questions.

18 DR. NELSON: Did you do any comparison with
19 any other label?

20 DR. SUAREZ-ALMAZOR: No. Just the
21 acetaminophen products.

22 DR. NELSON: So it was just in isolation.

1 Okay.

2 DR. NEILL: I have a question that's I think
3 both for Dr. Goulding and Dr. Ahmad, and I think it
4 really involves you checking my math.

5 I was listening to each of your
6 presentations to try and gather an estimate of the
7 incidence of adverse events, either measured as
8 hospital discharges, hepatotoxicity, calls to the
9 poison center, such as it was.

10 Dr. Goulding, in slide 12 of your
11 presentation, you report that in the most recent
12 time periods studied, there were 7.1 per 100,000
13 calls or 71 per million calls.

14 Dr. Ahmad, in slide 10 of your presentation,
15 you estimate the rate of discharges involving
16 hepatotoxicity to be .04 per 100,000 or 1.19 per
17 100,000.

18 So those rates, all expressed as per
19 100,000, in trying to relate those, Dr. Goulding's
20 are calls to a poison center, that's the highest
21 rate for which the denominator is presumably
22 anybody that might have access to the phone and

1 call the 800 number, 7.1 per 100,000. And then,
2 Dr. Ahmad, of those, 1.1 involve a hospitalization;
3 of those, .04 per 100,000 results in a
4 hospitalization that has an hepatotoxicity.

5 Given what you know about that epidemiologic
6 data, does that sync -- does that jibe with what
7 you know generally about safety of acetaminophen
8 single ingredient products in the general
9 population?

10 DR. AHMAD: With respect to NIS, as I
11 mentioned before, we did not exclude other
12 products. And, also, we were not able to
13 distinguish whether these are single ingredient
14 acetaminophen or combination products.

15 The other thing is unlike NPDS, NIS is a
16 hospitalization database. So I would imagine that
17 only a small number of patients or health care
18 providers or their caregiver who call a poison
19 control center ultimately go to the hospital and
20 are hospitalized.

21 So what I'm trying to say is those patients
22 may not be captured in the NIS database. So only

1 perhaps the serious cases are captured.

2 Did I answer your question?

3 DR. NEILL: Yes.

4 DR. AHMAD: Thank you.

5 DR. NEILL: Dr. Curry?

6 DR. CURRY: I can speak from our own
7 personal experience. I'm in a group of six
8 toxicologists and four fellows, and we have a
9 poison center that receives over 110,000 calls a
10 year, and we usually have 8 to 10 inpatients in the
11 hospital.

12 I looked at our data over the last couple
13 years and, for example, I believe in 2009, we had
14 about 43 calls, children who were chronically
15 receiving too much, according to parents who'd call
16 the poison center. Three were sent to the
17 hospital -- or three showed up at the hospital
18 after we told them they didn't need to or we sent
19 them in and they actually didn't need to go.

20 I remember in the early '80s occasionally
21 seeing a child who was overdosed with infant drops,
22 with confusions between elixir volumes and infant

1 drop volumes. Nobody in our group can remember
2 seeing such a patient in a long time, which made
3 me -- I was very reassured with the numbers that
4 were presented that appears the incidence has
5 fallen, because that's certainly our experience.

6 I should also say that I have had several
7 children die with acetaminophen on board who would
8 have been coded at discharge diagnosis with
9 acetaminophen toxicity over the last several years,
10 and none of them died from acetaminophen. They all
11 died usually from the concomitant opiates that were
12 with them or multiple other agents they were
13 taking.

14 So, again, the fact that you're coded
15 acetaminophen, since other diagnoses weren't
16 excluded, doesn't mean necessarily, by any means,
17 that the acetaminophen was the cause of the death,
18 and that's what was implied in the presentation.

19 DR. NEILL: Dr. Curry, you or the other
20 toxicologists can maybe help me, if you're more
21 familiar with the call center data. How does a
22 case relate to calls? Will a single case result in

1 multiple calls, and is that the common phenomena?

2 DR. CURRY: My experience is that different
3 poison centers can do things differently, but if
4 the database that's being queried is the American
5 Association of Poison Control Centers, we should
6 have someone from them speak specifically. But I
7 would assume that a case would be a human exposure,
8 although a case may also include people just
9 calling with informational calls, and I forget
10 exactly how it was set up back here.

11 DR. GOULDING: So calls can involve multiple
12 cases, but in the data we receive, we get unit
13 level. We get -- one call is one case.

14 DR. NEILL: Any other questions from the
15 committee?

16 [No response.]

17 DR. NEILL: Great. So the next presentation
18 will also be from FDA, from the Division of
19 Pharmacovigilance, which I think must win the award
20 as the best name for a division.

21 [Laughter.]

22 DR. NEILL: Dr. Waldron?

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FDA Presentation - Peter Waldron

DR. WALDRON: I can't take any credit for the name, but I like it, too.

My name is Peter Waldron. I'm a medical officer in the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology. Today I will be presenting the results of our division's analysis of adverse events in young children associated with the use of acetaminophen that were reported to the FDA, and I will briefly describe some highlights from the medical literature. I will start, though, with some background regarding the extent of use of this product and the nature of the adverse events, and then I'll end with our conclusions.

First, the background. This is an impressive number to me, that in a telephone survey done over the period of 1998 to 2007, so a long period of surveying, in a representative sample of U.S. households, they found that over any given seven-day period, that 23 percent of children in the under 24-month age group received at least one

1 dose of acetaminophen. And with regard to the
2 types of adverse events that are reported, the most
3 common one is an unintentional overdose, and these
4 represented 70 percent of the adverse events. And
5 of those adverse events, two-thirds of the
6 unintentional overdoses occurred in children under
7 the age of 12.

8 These last two bits of information were
9 reported in 2009 from an FDA epidemiologist, and
10 the first information -- and it's cited in the
11 handout -- was from Pediatrics, the journal, in
12 2009.

13 The adverse event reporting system, which is
14 the source of much of the data that I'll be
15 presenting, is a voluntary reporting system. It's
16 comprised of reports from consumers and from health
17 care providers who can submit information directly.
18 Some of you may know this system by the term
19 MedWatch, to which these reports are submitted.
20 The other source is these reports coming to the
21 awareness of a pharmaceutical company
22 representative. And then when these reports are

1 received by a pharmaceutical company, they are
2 required by regulation to report those to AERS.

3 This is a passive system in the sense that
4 we do not solicit the information. We merely
5 receive the information. It receives information
6 on human drug and therapeutic biological agents.
7 It works best to identify rare events. It doesn't
8 work well to identify very common events because
9 they're happening to everyone in the population,
10 and it would be hard to detect that as a new
11 signal.

12 It's always helpful to know the limits of a
13 method, and certainly AERS does have limitations.
14 First, we know that we do not detect all events.
15 Therefore, there is underreporting. There is
16 variation in the quality of the reports. It can be
17 a single page with not much information, and so too
18 little. It can be 15 pages with a lot of
19 information, that it's a challenge to detect the
20 important parts. And then there is the just right,
21 where the relevant data is present in an organized
22 fashion.

1 There are reporting biases to this dataset.
2 And this event, for example, where we're focusing
3 on acetaminophen, is likely to cause a reporting
4 bias of more reports with regard to acetaminophen
5 toxicity or concerns with that at least. Another
6 example would be product recalls, again, focusing
7 on a particular drug which could bias the reporting
8 to the AERS system.

9 It is difficult to attribute -- and
10 "attribute" here is a technical term meaning that
11 we're confident that exposure to a drug caused an
12 adverse effect. It's difficult to attribute events
13 which have a high background rate. And examples of
14 this would be a mild headache or a mild fatigue.
15 It's happening so frequently in the population,
16 it's hard to know that exposure to a drug was the
17 cause for that adverse event.

18 It's also difficult to attribute events
19 where there's a long period between the exposure to
20 the agent and that event. And what I'm most
21 familiar with, as an example, is second
22 malignancies in children with cancer who, maybe 5

1 to 10 years later, would develop that second
2 malignancy; obviously, tragic, but unless there is
3 a large number of events and a consistent finding,
4 it's hard to see that as related.

5 It is not useful for determining incident
6 rates. And since we've been talking about
7 baseball, we can think of the analogy of we know
8 how many hits, but we have no idea how many times
9 you were at bat, so that we can't then compare
10 within a class of agents; so that we couldn't
11 compare, for example, the adverse event frequency
12 of antipyretics or analgesics, because we don't
13 know the denominator. We don't know the number of
14 times at bat.

15 This search then was conducted with these
16 criteria. It included all serious -- and this is
17 the CFR, cited here, definition of serious,
18 domestic -- and so only U.S., not
19 foreign -- adverse events reported associated with
20 single ingredient acetaminophen products without
21 concomitant medications.

22 It is limited to children under the age of 2

1 or here as zero to 2, but if you had your second
2 birthday, you were not included. These were
3 reports that were received by the FDA between
4 January 1, 2000 and December 31, 2009. That does
5 not mean that these events occurred during that
6 time, only that the reports were received during
7 that time. Using those criteria, then, there were
8 a total of 92 serious adverse events, 89 of which
9 were nonfatal and three were fatal cases.

10 The fatal cases were in children ages 1, 18
11 and 22. There is an error in this line on your
12 slide set in the handout. It's 20, and that is
13 incorrect. It's 1, 18 and 22 months. The deaths,
14 although with limited information, appeared to be
15 due to unintentional overdose. The direct cause of
16 death was hepatic failure in each of these cases.

17 Although, again, the data was not perfectly
18 clear, our best interpretation was that it was
19 consistent with a greater than one day, so a more
20 than 24-hour period of this supra-therapeutic
21 dosing, and this would be officially classified
22 then as a medication error, and the next speaker

1 will address this in more detail.

2 The nonfatal serious adverse events captured
3 by the AERS system, the most common one was GI
4 system, which was nausea and vomiting. Rash and
5 allergic reactions were the next most common.

6 Just a comment on a couple of these others.
7 The convulsions and seizures were consistent with a
8 febrile seizure, seizure in a child with a known
9 neurologic disorder, and one child's seizure in the
10 context of a central nervous system infection. The
11 renal system effects were changes in urine color,
12 which resolved with withdrawal of the drug. There
13 is no specific data with regard to urinalysis.
14 Then I will skip to the hepatic, which were those
15 two cases that involved elevation of transaminases
16 and of bilirubin.

17 Then there is considerable literature, and
18 many of you in the audience, I'm sure, have
19 contributed to the medical literature. These are
20 only the barest of highlights for that and just
21 some representative.

22 First, we have been hearing about the

1 American Association of Poison Control Centers and
2 their annual reports, as well as the limitation of
3 the report, which provides the number of
4 administrations of N-acetylcysteine per year.

5 First, this data is reported as the youngest
6 age group is under 6. And so everyone under 6 is
7 lumped together. And the number here, the 337 per
8 year to 400 doses of N-acetylcysteine -- I should
9 say maybe courses of N-acetylcysteine administered
10 per year -- is a surrogate for a judgment of
11 considerable and, I would say, severe, using our
12 definition, hepatic toxicity. We don't claim that
13 this is equivalent, but even if this would only be
14 10 percent of this total number, that would
15 represent a true acetaminophen high risk situation.

16 Then relative to the number of cases
17 detected by the AERS system, two over that whole
18 10-year period versus if we would say, just for a
19 quick calculation, 40 per year over that five-year
20 period, you can see that there is a very different
21 number. And our best interpretation is that the
22 poison center data is probably more representative

1 of the public health burden than the data captured
2 by AERS.

3 Next, a paper that was published last
4 October also in Pediatrics was a systematic
5 analysis of children that had been enrolled in
6 clinical trials in which a dose of acetaminophen
7 was administered. This is a large number of
8 children, 32,000, more than 32,000. And so it's
9 always challenging to interpret data with very
10 large numbers.

11 One of the bits of information from the
12 table was that more than 98 percent of children
13 received a dose that was less than or equal to
14 60 milligrams per kilogram per day. I included
15 children -- or trials, I should say, if even part
16 of the children got at least that dose. The key
17 conclusion from that article was that
18 hepatotoxicity is rarely reported with therapeutic
19 dosing in a defined population.

20 Now, as with everything, there are limits
21 and what I felt were important limits to this study
22 were that, one, the 32,000 children were comprised

1 of 28,000 children from a single study. And so
2 that study then, in a sense, drove the statistics
3 from this whole group. And that study did exclude
4 children with any chronic disease, as well as
5 children with any extent of dehydration, actually
6 10 percent of dehydration, which is not more than
7 any -- which is more than any.

8 Then the same concern that has been brought
9 up before, this concept of assay sensitivity, the
10 ability to detect a problem if it's there. And the
11 large 28,000 children study used the assay for
12 toxicity of hospitalization for acute renal
13 failure, anaphylaxis, or development of Reyes'
14 syndrome. So those were the adverse events that
15 were captured and reported. And so there is then
16 the possibility that there were adverse hepatic
17 events that did not reach that threshold of
18 requiring hospitalization and fitting into one of
19 those other categories.

20 Last, what has already been cited, the
21 evidence-based guidelines developed by the American
22 Association of Poison Control Centers that are

1 their recommendations to their poison control
2 centers to recommend to a caller when they should
3 bring their child for evaluation in an emergency
4 department.

5 The first comment at the end of these
6 evidence-based guidelines was, first, that we don't
7 have much data and that more research to better
8 define the dose at which there is a need for
9 intervention is the most urgent need in this field.

10 The second thing, though, is the dose per
11 day and how this changes if that dosing has been
12 administered for more than 24 hours and then more
13 than 48 hours. So the concept that time with
14 administration of higher dose of acetaminophen is
15 relevant and maybe should be included in
16 guidelines.

17 So our conclusions, first, no new or
18 unexpected safety signals from AERS were identified
19 with pediatric acetaminophen use; second, the
20 National Poison Data System data show many more
21 cases of severe hepatic toxicity than AERS; and,
22 third, that overall data are insufficient to

1 provide a dose recommendation. And these are the
2 references.

3 Thank you.

4 DR. NEILL: Thank you.

5 We'd like to proceed with the FDA
6 presentation of Dr. Chan.

7 **FDA Presentation - Irene Chan**

8 DR. CHAN: Good morning. My name is Irene
9 Chan, and I'm a team leader in the Division of
10 Medication Error Prevention and Analysis. Today,
11 I'll be providing a medication error profile for
12 the pediatric use of oral acetaminophen and also
13 provide some points for consideration regarding how
14 to minimize medication errors in these patients.

15 So this presentation will consist of some
16 background information, including a description, a
17 brief description of the data sources that we
18 utilized to identify medication errors reports.
19 I'll present the results and analysis of our
20 adverse event reporting system database and
21 previous reviews completed by DMEPA that included
22 information from additional data sources. And,

1 finally, I'll provide some points for consideration
2 regarding how to minimize future medication errors
3 with pediatric use of acetaminophen and provide our
4 conclusions.

5 Pediatric patients are often given oral
6 single ingredient liquid or solid formulations of
7 acetaminophen from various manufacturers. Not all
8 solid oral formulations are labeled for use in
9 children. The ones that are noted here in red do
10 have labeling for use in children, and these
11 products are available in varying concentrations or
12 strengths, such as the ones I've listed here,
13 although historically these products have been
14 available in additional strengths and
15 concentrations on the market.

16 Liquid formulations are sometimes referred
17 to as drops, suspensions, elixirs, solutions or
18 syrups, often with these terms being utilized
19 interchangeably.

20 To gather medication error data, I did
21 search the Adverse Event Reporting System database,
22 otherwise known as AERS. This database includes

1 voluntary reports from health care providers and
2 consumers that are reported to the FDA MedWatch
3 system and their manufacturers. This database,
4 including its limitations, were reviewed by
5 Dr. Waldron in his presentation.

6 DMEPA was also asked to summarize four
7 previous reviews that we conducted. In addition to
8 AERS data, these reviews analyze pharmacovigilance
9 data from McNeil, as well as two poison control
10 centers that were also submitted by McNeil.

11 So I'll start by discussing the results and
12 analysis of the AERS database search that we
13 conducted.

14 We conducted a search of the AERS database
15 to identify medication errors involving pediatric
16 use of oral acetaminophen. We searched for
17 domestic reports within a 10-year period that
18 involved patients between the ages of zero to 13
19 years. We limited the route of administration to
20 oral and coordinated our product list with the
21 Division of Pharmacovigilance. Because we focused
22 our search for medication errors, we utilized the

1 MedDRA higher level group terms "medication errors"
2 and "product quality issues" in order to complement
3 the search that was conducted by the Division of
4 Pharmacovigilance.

5 We did not limit our patient outcomes for
6 our search, and we retrieved a total of 94 cases
7 with medication errors, and the following slides
8 will give descriptive statistics for these cases.
9 We also identified 120 cases of accidental
10 unsupervised ingestions, which will be discussed in
11 further detail near the end of this presentation.

12 The 94 relevant cases in AERS identified a
13 total of 95 medication errors, since one case
14 contained more than one medication error. This
15 table summarizes the type and number of medication
16 errors that we retrieved in our search. As you can
17 see in the table, overdoses were by far the most
18 common type of medication error identified,
19 followed by product labeling complaints, where an
20 error did not reach the patient.

21 Based on this observation, we'll be focusing
22 our discussion today on overdoses and the product

1 labeling complaints that were identified.

2 So this graph identifies that the AERS are
3 categorized by patient age group and then error
4 type. The X-axis represents age groups and the
5 Y-axis represents the number of cases. Within each
6 age group, overdose was the most common type of
7 medication error identified.

8 What's important to note in the graph is
9 that more than half of all medication errors
10 reported to AERS occurred in children less than
11 2 years of age. And, additionally, the largest
12 number of overdose cases occurred in children
13 6 months to less than 2 years of age, despite the
14 fact that there is no dosing information labeled
15 for children less than 2 years of age.

16 Of the 94 cases, 14 resulted in death, and
17 all of the deaths were due to hepatic failure
18 caused by overdose of acetaminophen. This table
19 summarizes the fatal and nonfatal cases by age
20 group. Five deaths occurred in patients in the
21 6-months to less than 2-years age groups, with the
22 children being treated for colds or other viral

1 illnesses when the overdoses occurred.

2 Seventy-four of the 94 cases were nonfatal
3 cases, with the greatest number occurring in the
4 6-months to less than 2-years age group. Sixty-six
5 of these 74 nonfatal cases were overdose medication
6 errors. However, due to lack of dosing information
7 in the cases, no apparent dosing trends could be
8 determined across the age groups.

9 For nonfatal overdose errors, both serious
10 and non-serious outcomes were identified. Serious
11 outcomes included liver damage, seizures, and renal
12 failure. However, it's important to note that
13 outcomes could not be definitively linked to the
14 administration of acetaminophen overdose.

15 Of the 14 fatal cases, 11 did not provide
16 enough details to determine why the medication
17 error occurred. The remaining four cases did
18 report a cause of error, and these will be further
19 characterized in the next few slides.

20 In the first case, an emergency room
21 physician discharged a 5-month-old infant with
22 instructions to the parent to administer one

1 teaspoon of infant Tylenol drops. These schedule
2 was not provided in this case. The product was
3 reported to have been administered to the infant as
4 prescribed, and the infant developed acute liver
5 failure and died.

6 In the second case, the mother ran out of
7 the usual formulation of acetaminophen and crushed
8 regular adult strength acetaminophen tablets into
9 her 9-month-old daughter's formula. The child
10 developed acute hepatic failure and died.

11 In the third case, a parent was instructed
12 to give a 22-month-old child one and a half
13 teaspoon of Children's Tylenol every four hours
14 following discharge. The child ended up receiving
15 one and a half teaspoon of infant Tylenol drops.
16 Therefore, instead of a 240 milligram dose, the
17 child received a 750 milligram. The number of
18 doses administered was unknown, and the child died
19 after developing hepatic failure. Follow-up
20 information revealed that the mother had seen a
21 nurse administer concentrated drops in the
22 emergency room before her child was discharged and

1 this led the mother to believe that that was the
2 formulation that should be administered to her
3 child.

4 In the fourth case, a physician instructed a
5 mother to administer three-quarter teaspoons of
6 Tylenol to her child. The age of the child was
7 unknown in this case and based on the report, it
8 appears the physician did not instruct the mother
9 on what formulation to purchase. The mother ended
10 up purchasing infant Tylenol drops and gave there-
11 quarter teaspoons every four to six hours, as
12 instructed. The number of doses administered was
13 unknown, and the infant developed hepatic failure
14 and died before receiving a liver transplant.

15 As mentioned earlier, DMEPA was asked to
16 summarize the findings of four previous reviews we
17 conducted. Consistent with the findings of our
18 AERS case series, the AERS data in the previous
19 reviews identified that improper doses were the
20 most common type of medication error, with the
21 majority being overdoses. Many improper dose
22 errors were due to confusion between concentrated

1 drops and other pediatric formulations.

2 Regardless of the severity of outcome
3 identified in the AERS database, we found
4 similarity in the causes of error reported. And in
5 the next few slides, I'll discuss those causes of
6 error that were identified in the AERS database.

7 The availability of multiple concentrations
8 and formulations of liquid acetaminophen was
9 identified as a major cause of medication error.
10 As this slide demonstrates, acetaminophen is
11 available in varying concentrations on the market,
12 which adds to parent confusion when selecting
13 products.

14 Therapeutic duplication was cited as another
15 cause of medication error. We received cases where
16 parents gave more than one single ingredient
17 acetaminophen formulation, such as both the
18 concentrated drops, as well as the children's
19 suspension. We also had cases where a single
20 ingredient acetaminophen product was given to a
21 child in addition to a combination product.

22 Another cause of overdose identified was the

1 use of adult formulations of acetaminophen in
2 pediatric patients, despite the lack of labeling on
3 these formulations indicating that they can be used
4 in children. Caregivers have crushed adult
5 formulations of acetaminophen to administer to
6 children and this demonstrates a lack of knowledge
7 regarding which formulations are appropriate for
8 administration to children.

9 Provider-related causes of overdose include
10 providers not specifying what formulation parents
11 should buy or use, and when confronted with a
12 multitude of options available over-the-counter,
13 it's reasonable to see how parents or caretakers
14 can be confused about what products are appropriate
15 for a child. Providers are also sometimes aware of
16 the various concentrations that are available on
17 the market, which can lead to miscalculation of
18 doses or confusing instructions being given to
19 parents.

20 Confusing dosing devices were identified as
21 a cause of overdose errors. Problems with devices
22 included doses not being clearly marked, such as in

1 the picture on your right, and devices being
2 capable of measuring larger doses than would be
3 needed for administration, such as in the picture
4 on your left.

5 Additionally, parents or caregivers may not
6 always use the devices enclosed with a medication.
7 When dosing devices are confusing, parents may
8 utilize dosing devices from other medications that
9 they prefer or simply use a household teaspoon to
10 try to administer doses.

11 DMEPA also identified six reports of
12 labeling complaints where an error did not reach
13 the patient. These reports included concerns that
14 dosing cups are not consistent across products or
15 do not measure out the correct volume of medicine.

16 We also received a report expressing concern
17 that there are no directions for children under
18 2 years of age. We identified one report where it
19 was noted that the chewable tablets were not
20 scored, although the directions did call for a
21 half-tablet as part of the dose, and this
22 particular report involved a store-branded product.

1 Additional medication error data sources
2 that were reviewed previously by DMEPA included
3 pharmacovigilance data from McNeil, as well as
4 poison control data from two regional poison
5 control centers.

6 From the poison control data submitted,
7 DMEPA reviewed 1,730 reports of pediatric exposures
8 to acetaminophen-containing product in children
9 zero to 11 years of age from January to December
10 2000, 544 of which involved errors of
11 maladministration. The majority of calls to the
12 two poison control centers involved single
13 ingredient acetaminophen pediatric formulations,
14 and the types of medication errors were consistent
15 with those that we identified in the AERS database
16 and the data did not identify any new types of
17 medication errors.

18 McNeil also submitted 117 reports of drug
19 misadministration received from January 1 of 1992
20 to August 31st of 2000. And of the 117 reports
21 forwarded by McNeil, 50 involved the infant Tylenol
22 drops. It was noted that 68 of the 117 reports

1 involved children less than 2 years of age.
2 Overall, 50 resulted in hepatic-related outcomes,
3 12 of which resulted in death and three of which
4 resulted in liver transplants.

5 The pharmacovigilance data from McNeil
6 identified improper dose errors as the most common
7 type of medication error, again, with a majority
8 being overdoses. Wrong time or frequency errors
9 involved consumers who gave consecutive doses, not
10 realizing that another family member had just
11 administered a dose. And in some cases, consumers
12 also did not follow the labeled directions for use.

13 During the time period of January 1st, 1999
14 to August 31st, 2000, McNeil received 2,209 dosing
15 inquiries for pediatric Tylenol products.
16 According to McNeil, inquiries involving children
17 2 years of age and involving children weighing
18 24 pounds accounted for 48 percent of their
19 consumer inquiries, and the majority of these
20 inquiries were related to infant Tylenol drops.
21 McNeil also reported that consumers indicated it
22 would be helpful to have dosing on the labels and

1 labeling for children less than 2 years of age.

2 Questions regarding whether to dose by age
3 or by weight were also received by McNeil. Several
4 consumers also requested information on the
5 equivalency of different pediatric formulations and
6 how to switch formulations if they ran out of their
7 usual formulation. There were also numerous
8 inquiries regarding the measuring devices included
9 in the package. Many caregivers were confused
10 about the capital letter T markings, believing that
11 the capital T meant tablespoon rather than
12 teaspoon.

13 Additionally, because physicians often
14 prescribed in teaspoons or cc's, consumers were
15 unable to determine how much medication to give
16 based on the usual markings on the enclosed
17 measuring devices supplied with the Tylenol
18 products. McNeil also received questions about
19 what a 24-hour dosing interval meant.

20 Our analysis of the information from the
21 additional data sources provided by McNeil
22 identified additional causes of medication error.

1 The following slides discuss causes either not
2 previously identified in AERS or those further
3 characterized in the new data sources.

4 Though not currently approved in the
5 tentative final monograph, many marketed
6 acetaminophen products include dosing charts that
7 reflect age, as well as weights, for children who
8 may not fall neatly into age or weight categories.
9 This can present confusion for parents, as was
10 identified in the consumer inquiry calls to McNeil.

11 It can sometimes be difficult to identify
12 the concentration of the medication on the
13 container label's principal display panel, which
14 makes it easier for parents to overlook the fact
15 that there is a difference in concentration between
16 products. This can be especially problematic in
17 households with children of varying ages, where
18 parents may have more than one concentration in
19 their medicine cabinet.

20 Therapeutic duplication leading to overdose
21 continues to be a problem in the pediatric
22 population. We have identified cases where parents

1 did not realize they were administering more than
2 one product that contained acetaminophen. Several
3 cases involved parents administering acetaminophen
4 with another cough or cold multi-symptom product
5 that also contained acetaminophen. And in some
6 cases, parents who were familiar with the brand
7 name Tylenol did not realize that the active
8 ingredient was acetaminophen. This can be
9 especially problematic when parents are confronted
10 with products whose family trade names have
11 traditionally been associated with ingredients used
12 to treat other indications.

13 On April 29th, 2009, the final rule for
14 organ-specific warnings changed the labeling
15 requirements by adding new warnings about liver
16 injury for those using acetaminophen. The rule
17 also required labeling changes to the principal
18 display panel, ingredient listings, and other
19 labeling information to highlight the presence of
20 acetaminophen. This rule became effective on April
21 29th, 2010 and DMEPA is continuing to monitor to
22 see whether this will change the reporting pattern

1 for overdoses.

2 We identified confusion among various units
3 of measure as a cause of medication error. Because
4 physicians often prescribed in teaspoons or cc's,
5 consumers were unable to determine how much
6 medication to give based on the usual markings of
7 the enclosed mediation measuring devices supplied
8 with the products.

9 In the next few slides, I'll provide some
10 points for consideration when determining how to
11 minimize medication errors associated with the use
12 of acetaminophen in the pediatric population, and
13 I'll end with our conclusions.

14 Existing safety data supports OTC marketing
15 of a single concentration for liquid pediatric
16 formulations of acetaminophen, and this
17 recommendation has been made by experts in various
18 forums. The Consumer Healthcare Products
19 Association recently released a press statement
20 indicating that industry was voluntarily
21 transitioning to one concentration of single
22 ingredient pediatric liquid acetaminophen medicine.

1 We recognize that voluntary changes by
2 manufactures can occur faster than the federal
3 rulemaking processes. However, voluntary
4 transitioning cannot ensure enforcement across all
5 manufacturers. Only amending the tentative final
6 monograph to limit the OTC marketing to a single
7 lower concentration for liquid pediatric
8 formulations of acetaminophen will allow the FDA to
9 ensure that all manufacturers are complying with
10 the safety measure.

11 While publishing the final rule for organ-
12 specific warnings may increase awareness about the
13 presence of acetaminophen in various products
14 marketed over-the-counter, DMEPA believes that
15 increased education for caregivers and providers
16 about the varying formulations, varying
17 concentrations, the presence of acetaminophen in
18 multiple products with different family trade
19 names, implications of therapeutic duplication, and
20 what formulations are appropriate for children is
21 still needed. Additionally, education targeted at
22 health care providers about recognition of the

1 signs and symptoms of acetaminophen toxicity may
2 help to minimize the devastating outcomes of
3 overdose errors in the pediatric population.

4 Our review of data demonstrates that
5 children down to 2 months of age are receiving
6 acetaminophen, since this is the age when
7 immunizations begin. However, we recognize there
8 are risks associated with children less than
9 6 months of age not receiving proper medical
10 attention for fevers. Therefore, adding dosing
11 information for children down to at least 6 months
12 of age should be considered so that this
13 information is readily available to parents.

14 Due to the confusion surrounding dosing
15 devices, it is clear that a single standardized,
16 calibrated measuring device packaged in all liquid
17 acetaminophen products is needed, especially once a
18 single concentration is implemented in the
19 marketplace. However, it's important to realize
20 that there's currently no mechanism for including a
21 standardized device under the monograph
22 regulations, because monograph products can go to

1 market directly without review by the agency.

2 When manufacturers include a dosing device,
3 some important things to consider in the design
4 include determining whether it's possible to
5 integrate a measuring device with a product
6 container closure to help minimize the risk of loss
7 of a measuring device or the inappropriate use of
8 another measuring device. Additionally, it's
9 important to ensure that there are easily visible
10 measurement markings. Also, the devices should not
11 be able to administer more medication than would be
12 needed for usual dosage.

13 Confusing and non-metric abbreviations
14 should be removed. When abbreviations are
15 utilized, they should be defined on the labeling
16 and consistent with the directions that are listed.
17 Additionally, validation of such a device would
18 need to be done through usability testing before
19 being introduced to the market.

20 Some of these measures are consistent with
21 the voluntary guidelines that were adopted by the
22 Consumer Healthcare Products Association in

1 November of 2009, as well as the recently finalized
2 FDA guidance for industry on dosage delivery
3 devices for orally ingested OTC liquid drug
4 products.

5 We have identified that there is currently
6 no single standardized dosing chart reflecting the
7 same units of measure across all manufacturers.
8 Having a single standardized dosing chart once the
9 market is limited to a single concentration of
10 liquid acetaminophen could reduce the confusion
11 that occurs when switching between different
12 products.

13 This would need to be coordinated with the
14 development of a standardized dosing device to
15 ensure additional confusion is not introduced into
16 the marketplace. Any proposed standardized dosing
17 chart would need to be validated through label
18 comprehension studies.

19 We identified 120 cases of accidental
20 unsupervised ingestions of acetaminophen in
21 children in our AERS search, and they represented
22 nearly 20 percent of all cases identified in our

1 search during the 10-year period. Causes included
2 misadministration by other young siblings,
3 medication tasting sweet or like candy, and caps
4 being removed by children, although it was unclear
5 in these cases whether they were child-resistant
6 caps.

7 From a regulatory perspective, there's
8 little that can be done to prevent
9 misadministration of drugs by other young siblings.
10 We also recognize that palatability is an important
11 consideration when it comes to medications intended
12 for use in the pediatric population. However, over
13 time, numerous reports have suggested that children
14 are able to open these bottles by themselves
15 without assistance from others. DMEPA finds this
16 to be an alarming trend and we recommend that all
17 manufacturers of pediatric acetaminophen
18 formulations evaluate their container closures and
19 ensure that they are child-resistant.

20 Additionally, manufacturers could investigate the
21 inclusion of a barrier in their package design that
22 prohibits the easy emptying of contents in the

1 event that children are able to remove the caps.

2 After analyzing the data from AERS, along
3 with the four previous reviews completed, it's
4 clear that pediatric patients using acetaminophen
5 have experienced overdose errors, and these
6 continue to be the type of medication error that's
7 most frequently reported to the FDA among all age
8 groups. More than half of medication errors
9 reported in AERS were in children less than 2 years
10 of age. Consistent with the medical literature,
11 overdoses of acetaminophen in children have led to
12 serious outcomes, including death.

13 Acetaminophen's ability to cause acute
14 hepatic toxicity is well known, and, as expected,
15 reports of liver injury due to overdose were
16 identified. Overdose medication errors can be
17 prevented and interventions should be targeted to
18 decrease these errors. Implementation of some
19 interventions do require a change in regulations.

20 This concludes my presentation.

21 **Clarifying Questions**

22 DR. NEILL: Thank you.

1 So we have 15 minutes for questions before
2 lunch. Keep your hands up.

3 Dr. Goldstein?

4 DR. GOLDSTEIN: I just have a question for
5 the last speaker and a comment. My question is,
6 unless I misheard, I thought you said something to
7 the effect that immunizations start at 2 years, and
8 I think you either meant 2 months or I misheard.

9 DR. CHAN: I apologize if I misspoke. But,
10 yes, it was 2 months of age is generally --

11 DR. GOLDSTEIN: Thank you. Which brings me
12 to my comment, which is that I appreciate the
13 question posed to us, to the committees, by the FDA
14 as to down to 6 months. But given the data that
15 we've seen, the recommendations in terms of
16 immunizations, and also going to almost anybody's
17 website, including the American Academy of
18 Pediatrics and McNeil, that there are dosing
19 recommendations down to 12 weeks.

20 I would like to suggest that we consider
21 either addending or changing the question for
22 tomorrow's discussion with a lower age limit being

1 either 8 or 12 weeks rather than 6 months, or at
2 least somehow including that lower age group where
3 the drug is used and there are clearly problems for
4 discussion.

5 DR. NEILL: Dr. Furness, do you want to
6 comment on changing the question?

7 DR. FURNESS: Yes. This is Scott Furness.
8 We don't have any intention of changing the
9 question mostly because our review of the medical
10 literature really seems to support the idea that a
11 fever associated with children younger than
12 6 months of age really seems to require medical
13 attention so that serious infections are not
14 missed. Febrile infants are, of course, at a
15 greater risk for systemic bacterial infections,
16 including sepsis, meningitis, urinary tract
17 infections and so on, and these infections may
18 present as fever without localizing signs.

19 Our understanding and review of the
20 literature suggest that these risks for these
21 systemic infections is really greatest in infants,
22 because the immune system is less mature and they

1 may have a very limited ability to localize and
2 contain an infection. So because of our
3 understanding of the literature right now, that's
4 not on the table.

5 DR. GOLDSTEIN: Well, as a pediatric
6 intensive care physician who took care of overdoses
7 for 22 years, and I'm sure Dr. Notterman and
8 Dr. Wright can second me on this, and your own AERS
9 database review shows that this remains a problem
10 in children. There's no question, yes, that,
11 ideally, children under 6 months of age who have a
12 fever who are being treated with Tylenol should be
13 seen by a physician. The reality is that doesn't
14 always happen and that the drug is used and that
15 there are problems.

16 So I would suggest that the group consider
17 if not changing the question, at least having a
18 focused discussion on the younger age groups so as
19 not to ignore the reality of the situation.

20 DR. FURNESS: And another option that we may
21 consider after this meeting would be to add
22 professional labeling for the less than 6-month

1 population. So that's something that we may
2 consider, but it wouldn't be necessarily label
3 dosing directions. It would be considered
4 professional labeling. We're considering that.

5 DR. GOLDSTEIN: Why would the American
6 Academy of Pediatrics include labeling down to
7 12 weeks if it was only used at the discretion
8 of -- I don't mean to beat a dead horse, but I
9 respectfully disagree with this approach.

10 DR. FURNESS: That's fine.

11 DR. NEILL: It sounds like we're going to
12 have a great discussion tomorrow.

13 [Laughter.]

14 DR. GOLDSTEIN: It will be like a Saturday
15 Night Live thing with Jane Curtin and Dan Aykroyd.

16 [Laughter.]

17 DR. NEILL: Yes; those of us of a certain
18 age.

19 DR. GOLDSTEIN: I get to be Dan Aykroyd.

20 [Laughter.]

21 DR. NEILL: Dr. Cohen?

22 DR. COHEN: Mike Cohen. In looking through

1 the briefing materials and then listening to
2 Dr. Chan just now, it just seems obvious to me that
3 so many of the issues that are causing the
4 fatalities, et cetera, we know about and we know
5 what to do, and that includes going to one
6 concentration and packaging changes that I read
7 about, and an abbreviation issue, which we've had
8 mix-ups between tablespoons and teaspoons. Just
9 the measure is enough to cause problems sometime.

10 I know that in the past, we have had
11 situations where there have been companies out
12 there that -- you alluded to the fact that there's
13 apparently not a regulatory path to address these
14 things that we know so well. And I know we have
15 had problems. We had a company make a 16 ounce
16 bottle of acetaminophen 100 milligram per
17 milliliter. McNeil Consumer had the infant drops,
18 and they put cusps in it so you couldn't pour it
19 out. And they made that available, it was my
20 understanding, to other companies, but no one else
21 adopted that, that I know of anyway. So that
22 continued to be a problem.

1 I don't understand how we cannot have some
2 way of addressing in the monograph or some
3 regulatory path to make sure that everyone follows
4 these issues. So is there a way to do that would
5 be my question.

6 DR. FURNESS: This is Dr. Furness. The
7 short answer is that we don't have a mechanism to
8 globally require specific dosing devices with the
9 acetaminophen products. If we had to go out with a
10 regulation that requires that this formulation
11 requires this dosing device, it, by definition, is
12 outside the realm of the OTC monograph system, and
13 it would require an OTC NDA, which is very
14 possible. But under the monograph system, there is
15 no mechanism for that.

16 DR. COHEN: I don't know how we can continue
17 letting all this go on without assuring that it's
18 going to be 100 percent across the board with all
19 companies. So if that has to be done, then I think
20 that's needed.

21 DR. NEILL: Dr. Wright?

22 DR. WRIGHT: Just a quick question for

1 Dr. Pham [sic]. The fourth fatal case from AERS,
2 was there an age on that one? You mentioned it was
3 an infant. So I'm assuming it's under age 1. But
4 was there an age associated with that?

5 While you're looking that up, I just wanted
6 to dovetail on what Dr. Rakowsky mentioned earlier
7 about the practice of the convenience dose. I
8 think one of the root causes in one of the other
9 fatal cases that you mentioned was a confusion by
10 the parent based on the dose that had been
11 administered in the emergency department prior to
12 discharge and confusion around that, despite the
13 fact that there has been a marked decrease in other
14 areas.

15 The hospital emergency department remains a
16 place where administration of acetaminophen prior
17 to discharge or even going home with convenience
18 doses continues, and I was struck by that root
19 cause for at least one of your fatal cases.

20 DR. CHAN: In the particular case you're
21 referring to, the fourth fatal case, the age of the
22 child was unknown, or the infant was unknown, so we

1 can't comment on that.

2 With regard to the case where you're
3 mentioning -- just to clarify, the follow-up
4 information that was reported to the agency, it was
5 found that because the mother had observed the
6 nurse administering that particular concentration,
7 that was what led the mother to believe that was
8 what she should purchase once the child was
9 discharged.

10 DR. NEILL: Dr. Griffin? I've got
11 Drs. Griffin, Reidenberg, Rosenthal, Farber,
12 Notterman, and I think Parker just raised her hand,
13 and about six minutes left for discussion. We're
14 going to have time later today for discussion and
15 then tomorrow as well.

16 If we're not able to get to all of your
17 questions before lunch, please write them down or
18 come find me. If you really feel it's important to
19 do now, bring it to my attention before we break
20 for lunch.

21 Dr. Griffin?

22 DR. GRIFFIN: Thanks. Marie Griffin.

1 Maybe this goes for Dr. Chan. I'm
2 wondering, a medication error won't occur if the
3 medication is not given. We talked about a little
4 bit -- we heard about indications for treating for
5 fever, but do parents really know that all fevers
6 don't have to be treated, and who is responsible
7 for that kind of education? We're having
8 increasing use of these medications in children.
9 Is that appropriate or not? How do we get a handle
10 on that?

11 DR. CHAN: I don't know if I'm best
12 qualified to answer this. I think education
13 efforts is something that really needs to be
14 approached from all sides of the story.

15 Certainly, the agency has some
16 responsibility, manufacturers have some
17 responsibility. I'm speaking from my own
18 observations. But I think in terms of -- I
19 mentioned some of the issues, that it seems, based
20 on the data we receive, parents don't understand
21 what formulations they should be using. They don't
22 understand that there are differences in

1 concentration.

2 When you get family trade name products,
3 such as Dr. Cohen had mentioned about the Triaminic
4 product, for example, parents are familiar with a
5 specific family name that has always been
6 associated with a set of ingredients. So all of
7 this is really the responsibility of multiple
8 players.

9 DR. GRIFFIN: I'm sorry. I was sort of
10 going back a step, like not every fever needs to be
11 treated.

12 DR. CHAN: Right.

13 DR. GRIFFIN: So how do parents know when
14 they need to treat a fever and who sort of said we
15 have advertising that tells parents they can use
16 medicines and how to use it, but how do they make
17 that decision about to use it in the first place?

18 DR. CHAN: I might refer to one of my
19 colleagues to answer.

20 DR. HERTZ: So I don't think it's the FDA's
21 regulatory authority to be able to educate families
22 on when to treat symptoms. I think that through

1 proper labeling, we can provide a path for safe and
2 effective dosing recommendations for when it's
3 indicated. But I think perhaps it would be a good
4 idea for some of the folks here at the committee,
5 who I think may be better qualified to address how
6 does that education get to parents --

7 DR. NEILL: I'm actually going to take the
8 prerogative to move us to the next couple of
9 questions, because this sounds to me like an
10 anthropological discussion, which, in my practice,
11 the first answer is the mother, the next answer is
12 the grandmother, and all science be damned after
13 that.

14 [Laughter.]

15 DR. NEILL: So we can, of course, come back
16 to this, and I do appreciate that that is an
17 extraordinarily important question, just one that I
18 don't think we're going to answer before lunch.

19 Dr. Reidenberg?

20 DR. REIDENBERG: Reidenberg. I'm curious if
21 there's any data on educational level of the
22 parents of the children who had serious overdose.

1 And the reason I'm asking that is that in the study
2 of the focus groups that we were told about, the
3 majority of the members of the focus groups had
4 either bachelor or advanced degrees, all the others
5 were high school graduates, some with some college.

6 My experience is that there's a huge
7 difference between disclosure and informing, and if
8 we read our IRB-approved consent forms in research,
9 they fully disclose and do a lousy job of
10 informing.

11 So where we heard about requests for more
12 information on the labeling, I think it would be
13 helpful to know whether the inadvertent continuing
14 overdoses that cause the serious problem were
15 people with more education or less education and
16 understanding of labeling all together.

17 DR. CHAN: Dr. Chan. Specifically, in our
18 AERS search, that information was not provided. As
19 Dr. Waldron mentioned in his presentation, there
20 are a lot of limitations to the AERS database. So
21 educational level of the parents or caretakers was
22 not something that we were able to determine.

1 DR. REIDENBERG: How about all the other
2 databases?

3 DR. CHAN: Again, from the data that was
4 submitted by McNeil, that information, if it was
5 available, was not provided to us, but they would
6 probably be able to address that when they speak
7 this afternoon.

8 DR. NEILL: Dr. Farber?

9 DR. FARBER: Neil Farber. At our last NDAC
10 meeting, it was recommended that there be a uniform
11 dose, uniform concentration for both infants' and
12 children's liquid acetaminophen. I was wondering
13 if anything had happened about that since your data
14 are reporting up to 2009.

15 DR. CHAN: Dr. Chan again. As I mentioned
16 in my presentation, the Consumer Healthcare
17 Products Association did release a press statement,
18 and I believe, if I'm recalling correctly, that
19 they anticipate by mid-2011, so pretty much any day
20 now, voluntarily industry will be moving to the
21 single concentration. But as I mentioned, right
22 now, there's no regulatory pathway that allows the

1 FDA to oversee that.

2 DR. NEILL: Dr. Furness? Dr. Kweder, did
3 you want to augment that?

4 DR. KWEDER: Sure. That is something that
5 could be -- we could limit in a monograph, we could
6 limit it to a single concentration. That is one of
7 the options that we would have before us. We could
8 limit tablet size. We could limit to a single
9 concentration. As we address dosing for
10 pediatrics, that could be part of the
11 recommendation.

12 DR. NEILL: So, Dr. Notterman, then
13 Dr. Parker.

14 DR. NOTTERMAN: Actually, my question is
15 also a follow-up to that. First, I want to mention
16 this was a terrific presentation, Dr. Chan, very
17 informative. Thank you.

18 On your slide 37, as we just heard, you
19 suggest that we might want to have a single dosage
20 for liquid formulation, and I wondered if you had
21 one in mind.

22 [Laughter.]

1 DR. CHAN: Well, as far as concentration
2 goes, as we know, that probably the two highly
3 publicized ones that we've been speaking about
4 would be the 80 milligram per .8, although there is
5 also an 80 milligram per 1, and then the 160
6 milligram per 5 ml, which is a less concentrated
7 formulation that we see with the children's
8 suspension.

9 So I am not personally aware, although other
10 colleagues may be able to speak otherwise, of
11 studies that we have done to identify the ideal
12 concentration, although when you look, especially
13 in the 6-months to 2-years age range, a lot of
14 these overdoses were due to confusion, where kids
15 were getting the infant drops in an overdose
16 concentration. Some of those did lead to serious
17 adverse outcomes.

18 So it would follow that if an overdose were
19 to still occur with a less concentrated
20 formulation, perhaps the outcomes may not be as
21 devastating. But, again, I'm not certain.
22 However, McNeil may have more information related

1 to whether they had looked into this information
2 this afternoon. I would defer to them.

3 I do know that the Consumer Healthcare
4 Products Association, in their press release,
5 indicated that the move would be to the
6 160 milligram per 5 ml concentration.

7 DR. NEILL: I heard that as a no, they're
8 interested in our advice.

9 DR. NOTTERMAN: I heard that as a maybe, and
10 I think we've made up our mind, but we don't want
11 to say yet.

12 [Laughter.]

13 DR. NEILL: Dr. Parker?

14 DR. PARKER: Thank you. A series of very
15 good presentations. Thank you all for all the work
16 on them. So I just want to make sure I understand,
17 from a process standpoint, that I heard this
18 correctly. Me and my little world of healthy
19 literacy, I'm always trying to make sure maybe I
20 can at least figure out where the clarity is. So
21 let me see if I can get this right.

22 So we do have under the monograph process

1 the ability to look at limiting to a single
2 concentration.

3 DR. FURNESS: Scott Furness. That's
4 correct.

5 DR. PARKER: Great. That would be a yes.
6 We do have the ability under the monograph process
7 to look at a single standardized chart regarding
8 dosing.

9 DR. FURNESS: That's correct.

10 DR. PARKER: Those are currently two things
11 we don't have that we could do. It sounds like
12 there is support for the fact that those would be
13 improvements.

14 The third question, always the devil in the
15 details, where are we with the monograph process in
16 terms of looking at a standardized dosing device
17 that would match a potential standardized dosing
18 chart with potentially a standardized dosing
19 concentration that might give us an integrated
20 approach to potentially improving things?

21 DR. FURNESS: In terms of the dosing
22 devices, as I said earlier, we cannot actually

1 require a very specific dosing device. Having said
2 that, the Office of Compliance has made great
3 strides recently. They just published a finalized
4 guidance on dosing devices, stating that whatever
5 is contained on the dosing directions, the actual
6 decrements also have to match on the dosing device.

7 So you have to have the label and dosing
8 device having matching and preferably minimization
9 of any other dosing measurements. So that actually
10 went to final just a few weeks ago.

11 DR. KWEDER: It's independent of the
12 monograph, but there are things that we can do, is
13 the answer.

14 DR. PARKER: So the dosing device
15 standardization itself is independent of the
16 monograph, but we could look at -- what makes sense
17 is to connect the dots somehow.

18 DR. FURNESS: Right.

19 DR. PARKER: So making something that
20 makes -- what would be useful within the monograph
21 process to connect the dots from the device to the
22 label to the concentration? Is there anything that

1 we do that helps connect that under this process?

2 DR. FURNESS: Under the monograph, we could
3 connect the label with the concentration. The
4 dosing device, we can provide recommendations, but,
5 again, we can't require the --

6 DR. KWEDER: We could require specifics. We
7 could require that it be administered with a device
8 with such properties.

9 DR. PARKER: Okay. So there is something
10 there. Okay. Thank you.

11 DR. NEILL: One last comment before we break
12 for lunch.

13 DR. HOLQUIST: Carol Holquist, FDA. One
14 thing you could do under the monograph is to
15 specify the dose in terms of a specific unit of
16 measure. So if it was a milliliter, and that's
17 what you wanted, that's what you could put in
18 there, and then hopefully the device would match
19 whatever is on the label.

20 DR. KWEDER: Exactly.

21 Can I make one final comment? I felt like
22 there was a loose end about the recommendations for

1 dosing for pediatric patients down to, say,
2 12 weeks or 6 months.

3 Some of the presentations this morning -- we
4 are constantly confronted with dosing
5 recommendations, whether they are by companies or
6 by professional groups, or individual practicing
7 physicians, or moms, that are outside of the data
8 that we have available to us to establish that a
9 product is safe and effective for that particular
10 group of patients. And in this case, most relevant
11 is the young patients under 6 months.

12 So regardless of what -- and it is
13 something -- there's a tension there about
14 should -- because an academy or a professional
15 society recommends dosing for a specific group,
16 does that mean that FDA labeling should also have
17 that same information in it?

18 Our regulations are clear. We can only
19 label products for the population in which the
20 product has been found to be safe and effective.
21 But there is this tension, and we are engaged with
22 a lot of those organizations and societies to try

1 and bring about the best education possible to
2 assure that products are used safely and within
3 what we understand about the data to support that
4 use.

5 DR. NEILL: So on that note, we are going to
6 break for lunch. We are going to reconvene again
7 in this room in one hour at 1:35. Please take your
8 personal belongings with you, as the room will be
9 secured by FDA staff during the lunch break, and
10 you will not be allowed back into the room until we
11 reconvene.

12 Panel members, remember, there should be
13 discussion of the meeting during lunch amongst
14 yourselves or with any other members of the
15 audience.

16 There is a buffet lunch downstairs in the
17 hotel restaurant that committee members can charge
18 to their room or you can go outside. There's no
19 pre-setup group lunch available.

20 (Whereupon, at 12:37 p.m., a lunch recess
21 was taken.)

22

A F T E R N O O N S E S S I O N

(1:35 p.m.)

1
2
3 DR. NEILL: Welcome back, everybody. I'd
4 like to get started with this afternoon's open
5 public hearing. We have industry presentations
6 that we'll dive right into with Dr. Barbara
7 Kochanowski.

8 **Industry Presentation - Barbara Kochanowski**

9 DR. KOCHANOWSKI: Good afternoon. Thank you
10 for the opportunity to speak to you today about the
11 important issue of helping parents and caregivers
12 safely administer acetaminophen-containing
13 medicines.

14 My name is Barbara Kochanowski, and I'm Vice
15 President of Regulatory Affairs at the Consumer
16 Healthcare Products Association, or CHPA. I'm here
17 today representing the association and our member
18 companies, the manufacturers of over-the-counter
19 pediatric acetaminophen medicines, whose names you
20 see on this slide. These manufacturers represent
21 nearly the total acetaminophen single ingredient
22 product market.

1 I just want to clarify up front, as you
2 think about our group of companies and the actions
3 we are taking. We identified only one other
4 company that is not a CHPA member who is making
5 single ingredient liquid acetaminophen for
6 children. We've spoken with them and they are, in
7 fact, also making all of the changes that we're
8 talking to you about today. And I can answer
9 further questions if you have any about that.

10 Our members strongly support FDA's convening
11 of this advisory committee meeting to gain input on
12 pediatric dosing of acetaminophen, and we hope our
13 presentations today will enable this committee to
14 support important additions to the label.

15 Acetaminophen is the most commonly
16 recommended medicine by physicians to treat pain
17 and fevers, and it's used frequently by parents and
18 caregivers to effectively treat children. As a
19 result of this, there is a need for additional
20 dosing information on the OTC label.

21 Today we will present data and information
22 to help you in your discussions of the four

1 questions FDA has posed. The data we present will
2 be organized by each FDA question.

3 Regarding our position on weight-based
4 dosing and adding dosing information on the OTC
5 labels for children from 6 to 23 months, which is
6 addressed as part of FDA questions 1 and 2, we
7 support adding dosing directions for children
8 6 months to under 2 years of age on the OTC labels
9 of children to acetaminophen medicines, and we
10 believe weight-based dosing should be required on
11 OTC labels for children under 21 years of age, as
12 dosing according to a child's weight is the more
13 consistent and accurate method of dosing children.
14 For parents and caregivers who don't know a child's
15 weight, age-related directions should remain on the
16 label.

17 As you've heard from FDA, many of these
18 recommendations are similar to those of previous
19 advisory committees that have considered pediatric
20 dosing of OTC drug products.

21 Historically, dosing information for
22 children under 2 had been provided to parents via

1 health care providers, such as primary care
2 physicians, pediatricians, and pharmacists.
3 Currently, again, as you heard this morning, dosing
4 on the OTC label for children now says ask a
5 doctor. But more recently, dosing information for
6 children under 2 has become widely available
7 through parent-focused websites such as these on
8 the screen.

9 Unfortunately, some of these sites have
10 incorrect dosing information. So what was once
11 very tightly controlled information given to
12 parents only by health care practitioners is now
13 widely available, but not on product labels, where
14 and when parents need it.

15 For many years now, the manufacturers of
16 children's acetaminophen have voluntarily put
17 weight-based dosing on their medicines for children
18 2 and over. This is in addition to age-related
19 dosing. So parents are used to seeing and using
20 this information.

21 This is an example of such a chart on one
22 product and we believe the addition of weight-based

1 dosing should be made mandatory as part of the OTC
2 monograph for acetaminophen liquid products for
3 children.

4 While weight-based dosing for acetaminophen
5 is not part of FDA's OTC drug monograph, the FDA
6 does recommend this approach for over-the-counter
7 medicines. It's actually on the FDA website as
8 part of its checklist for parents for choosing
9 over-the-counter medicines for children.

10 Our support of providing both dosing
11 instructions for children 6 months to under 2 years
12 and weight-based dosing for all children is aligned
13 with the recommendations of leading medical
14 organizations, like the American Academy of
15 Pediatrics.

16 In 2009, an online study was conducted of
17 200 pediatricians. When asked, "Will dosing
18 instructions on the label for children 12 to
19 23 pounds or 6 to 23 months of age increase
20 caregivers' ability to dose accurately," more than
21 90 percent said yes.

22 Weight-based dosing is also preferred by

1 pediatricians. In a 2011 survey by McNeil Consumer
2 Healthcare, pediatricians strongly favored
3 inclusion of weight-based dosing and dosing under
4 2 years of age on OTC product labels.

5 We realize that adding this information to
6 the label is just one element of ensuring the safe
7 use of our products, which brings me to question 3,
8 minimizing medication errors.

9 Since the previous advisory committee
10 meetings on acetaminophen, CHPA and our member
11 companies have been advancing pediatric
12 acetaminophen safety on our own and with partner
13 organizations. Our member companies have improved
14 OTC product labels and dosing devices by
15 highlighting the active ingredient and
16 standardizing the volumetric measures used to
17 convey dosing information, and all of our companies
18 have agreed to convert their pediatric single
19 ingredient liquid acetaminophen medicines to one
20 concentration and improve packaging, as well as
21 standardize the dosing devices for these products.

22 Specifically, all pediatric liquid

1 acetaminophen medicines will consist of a single
2 concentration of 160 milligrams per 5 milliliters.
3 Manufacturers will no longer offer concentrated
4 infant drops. This change follows a significant
5 long-term investment in new equipment and
6 manufacturing validation begun last year.

7 The new infant medicines will have flow
8 restrictors to reduce accidental ingestions and
9 syringes for dosing devices to help reduce
10 medication errors. Children's products will be
11 sold with dosing cups with standardized markings.
12 Markings on the cup will match doses on the labels.
13 Milliliter is the preferred unit of measure, with
14 teaspoon as a secondary measure.

15 This shows you one example of what a flow
16 restrictor looks like. In this case, the flow
17 restrictor would limit the amount of medicine a
18 child could access during an unsupervised
19 ingestion. These product enhancements are
20 scheduled to come on the market starting this
21 summer for some manufacturers and progressing into
22 early 2012.

1 These important changes, the move to single
2 concentration, flow restrictors, and new dosing
3 devices, will be supported by outreach to health
4 care professionals and consumers. We'll be working
5 with health care providers to whom parents look for
6 guidance, those named here, to update their dosing
7 charts and educational materials.

8 Finally, to further increase safe use of
9 these medicines, our companies are testing the
10 value of adding an acetaminophen ingredient icon to
11 the OTC drug facts label. An icon could
12 potentially reduce the chances of multiple
13 acetaminophen-containing medicines being used
14 concomitantly by alerting caregivers to the
15 presence of acetaminophen.

16 This is one design that has shown promise in
17 early consumer and health care provider research.
18 Following additional validation research, results
19 will be discussed with FDA, along with possible
20 implementation strategies, for both OTC and RX
21 acetaminophen-containing products.

22 In addition to improving the label, we also

1 have focused our attention on educating parents on
2 how to safely dose and store acetaminophen. To
3 reduce accidental ingestion, CHPA and our companies
4 are working with the CDC, FDA, and important health
5 care and pediatric associations to create education
6 campaigns to increase ingredient awareness and
7 educate parents on how to use and store
8 acetaminophen-containing medicines properly. I
9 will share these efforts with you in more detail a
10 little later.

11 Everything I've just outlined for you is in
12 line with key recommendations made by FDA earlier
13 this morning on mitigating medication errors.
14 Regarding the last question on whether solid oral
15 dosage forms should be restricted to a single
16 strength, we do not believe this is warranted. As
17 you will hear later, manufacturers receive very
18 infrequent calls about this question, which
19 indicates that there does not appear to be
20 confusion between the 80 and 160 milligram
21 strengths.

22 Before I introduce our speakers, I want to

1 reiterate that we're here to help ensure that our
2 medicines are used safely by parents and
3 caregivers. We take the trust physicians, medical
4 associations and parents have in our medicines very
5 seriously, which is why we are committed to helping
6 parents and caregivers administer these medicines
7 to their children in a safe and timely manner. But
8 to do that, parents need clear dosing information
9 on the label where they can easily access it.

10 Today we have several speakers who will
11 share data and their professional insights about
12 the efficacy and safety of acetaminophen in
13 children.

14 Drs. Cathy Gelotte and Ed Kuffner from
15 McNeil Consumer Healthcare will present data on
16 acetaminophen PK, efficacy, safety, weight-based
17 dosing, and the solid pediatric dosage form.

18 Dr. Randall Bond, a pediatrician, poison
19 center director, and emergency room physician with
20 30 years of experience, will share his insights on
21 acetaminophen dosing and improving the safe use of
22 these medicines.

1 Then I will come back to discuss our latest
2 programs and ongoing industry activities to ensure
3 the safe use of our products.

4 We also have the following experts with us
5 today to answer topic-specific questions, and I'll
6 point to two in particular. Dr. Rick Dart is also
7 a poison center director. So in addition to
8 Dr. Bond, Dr. Dart is here. You've seen him
9 referenced on some of the papers shown earlier.

10 So given the interest in poison center data,
11 you may want to re-ask or find some questions for
12 these individuals. Also, Tony Temple, who is also
13 referenced in the dosing paper that's often quoted,
14 is here with us, also, as an additional expert.

15 So with that, now I'd like to turn the
16 presentation over to Dr. Cathy Gelotte, Senior
17 Director of Clinical Pharmacology at McNeil
18 Consumer Healthcare, to answer the first part of
19 FDA's second question related to the
20 pharmacokinetic basis for acetaminophen dosing.

21 **Industry Presentation - Cathy Gelotte**

22 DR. GELOTTE: Good afternoon, everyone. In

1 the next series of slides, I'll highlight some main
2 findings from two pharmacokinetic analyses of
3 pooled data from McNeil pediatric and adult
4 studies. The purpose of these analyses was to
5 further evaluate the pharmacokinetics of
6 acetaminophen in children 6 to 23 months of age in
7 support of new OTC product labeling.

8 My presentation will focus on the following
9 key points. First, acetaminophen pharmacokinetics
10 has been widely studied across the pediatric
11 population. However, children 6 to 23 months of
12 age have not been evaluated as a cohort. I will
13 provide this evaluation today.

14 For children 6 to 23 months, the integrated
15 pharmacokinetic analysis showed that when
16 acetaminophen is dosed at 10 to 15 milligrams per
17 kilo, exposure or AUC is similar to that in
18 children 2 to 11 years.

19 Finally, the analysis of pharmacokinetic and
20 pharmacodynamic data showed that the relationship
21 between acetaminophen concentrations and fever
22 reduction is the same in both pediatric groups.

1 These results strongly suggest that similar drug
2 response and physiological response.

3 Before discussing the results of the
4 analyses, I'd like to summarize some learnings from
5 published research in children. Investigators have
6 developed population pharmacokinetic models that
7 assess factors that may affect acetaminophen
8 clearance, which is a measure of the rate of drug
9 removal.

10 This is important because information from
11 these models can be used to make adjustments in
12 pediatric doses, where necessary. Body size was
13 identified as the most influential factor affecting
14 acetaminophen clearance when analyzing pediatric
15 data, followed by age for neonates and young
16 infants. Neither gender nor race were found to
17 affect clearance or other parameters in these
18 models.

19 Next, I'd like to discuss the results of the
20 integrated analysis of oral pharmacokinetic data
21 across multiple McNeil pediatric and adult studies.
22 This analysis was undertaken to evaluate whether

1 the 10 to 15 milligram per kilo dose is an
2 appropriate OTC dose for children 6 to 23 months.
3 This table is the number of subjects in the three
4 age groups and the two dose levels that were
5 included in the analysis. The area under the
6 concentration time curve, AUC, was selected as the
7 primary measure of acetaminophen exposure for this
8 analysis, because it's related to oral clearance
9 and the administered dose.

10 In half of the pooled studies, children and
11 adults were administered the 10 to 15 milligram per
12 kilo dose twice as an acetaminophen oral liquid
13 four hours apart. The mean pharmacokinetic profile
14 for children 6 to 23 months is shown in this figure
15 with plasma concentrations measured over eight
16 hours.

17 For comparison, mean pharmacokinetic
18 profiles for children 2 to 11 years from two
19 studies are included and highlighted in blue. We
20 see that the profiles for the 10 to 15 milligram
21 per kilo doses are consistent between these
22 pediatric age groups.

1 For comparisons with adults, mean
2 pharmacokinetic profiles from three studies are
3 overlaid using white symbols and lines on the same
4 figure. We see that the overall shape of the
5 acetaminophen concentration time curve is
6 consistent with the pediatric age groups and
7 replicated across studies.

8 The area under the curve and maximum
9 concentration, C_{max} , for one dose were estimated
10 for each child and adult using standard methods.
11 They were also estimated for the 20 to 30 milligram
12 per kilo dose, but were divided by two in the
13 pooled analysis. This standardization is
14 acceptable for acetaminophen at low doses.

15 The acetaminophen exposure metrics were
16 pooled across studies and are summarized by age,
17 with AUC on the left panel of box plots and C_{max} on
18 the right. In each box, the median AUC or C_{max} is
19 the line between the 25th and 75th percentiles, at
20 the bottom and top sides of the boxes. These box
21 plots show that acetaminophen exposures for
22 children 6 to 23 months and 2 to 11 years are

1 comparable when dosed at 10 to 15 milligrams per
2 kilo. Cmax and AUC exposures appear only slightly
3 higher for the adult group, but these differences
4 would not be considered clinically meaningful.

5 Results from the statistical analysis
6 comparing standardized acetaminophen exposure for
7 children 6 to 23 months with older children and
8 adults are illustrated by this figure. In the
9 analysis, the ratios of geometric AUC and Cmax
10 means for children 6 to 23 months, relative to a
11 reference group, are constructed. These ratios are
12 plotted in the figures as point estimates along
13 with the 90 percent confidence intervals.

14 Acetaminophen exposure would be considered
15 equivalent to a reference when the mean ratio and
16 90 percent confidence intervals fall within the
17 boundary limits of 80 to 125 percent, shown here as
18 white dashed lines.

19 When compared with children 2 to 11 years
20 old, the intervals for both standard AUC and Cmax
21 fall within the boundaries, indicating equivalent
22 exposures for the 10 to 15 milligram per kilo dose.

1 When compared with adults as the reference group,
2 the intervals extended below the lower limit
3 indicating that acetaminophen exposure is shifted
4 lower in children 6 to 23 months for the same dose.
5 However, I'd like to point out that the ratio of
6 AUC means is about 90 percent.

7 This figure shows a scatter plot of
8 individual standardized AUC for children and adults
9 on the log scale with the regression through the
10 observed values. Results of a linear regression
11 analysis of log AUC by age found that acetaminophen
12 exposure for the 10 to 15 milligram kilo dose
13 increased only slightly from 6 months to 50 years.

14 Although the slope for the full range of
15 ages was positive, it was not statistically
16 significant. These findings are consistent with
17 the previous box plots and equivalence analysis in
18 which acetaminophen exposure in children 6 to 23
19 months is similar to that in children ages 2 to
20 11 years, but slightly lower compared with adults.

21 Now, I'd like to turn your attention to the
22 relationship among dose, plasma concentrations, and

1 drug response. We know that the dose concentration
2 process is described by pharmacokinetics and that
3 the dose-response by efficacy trials. These
4 relationships are often studied separately.

5 Clinical researchers have long recognized
6 that drug concentrations are related to therapeutic
7 responses. To gain insight from the concentration-
8 response relationship, quantitative tools have been
9 developed to estimate EC50, which is the drug
10 concentration that produces 50 percent maximum
11 response.

12 The EC50 has clinical application because it
13 can tell us about the relative drug potency. Its
14 value depends on drug properties, such as
15 distribution and receptor affinity, and biological
16 properties, such as receptor density and
17 physiological response.

18 In this slide, I'd like to illustrate the
19 linked relationship between acetaminophen
20 concentration and fever reduction by using actual
21 data from one subject as an example. In this
22 figure, plasma concentration is shown for eight

1 hours after an oral dose in a 20-month-old female
2 subject. We see that concentrations increase to
3 the maximum around one hour, then decrease
4 exponentially. The modeled pharmacokinetic curve
5 is overlaid on the measured values.

6 Likewise, temperature measurements for the
7 same child are shown for eight hours using the
8 right vertical scale. The modeled pharmacodynamic
9 curve is overlaid on the measured values. We see
10 that changes in body temperature are associated
11 with changes in concentrations.

12 Pharmacodynamic models have been linked to
13 pharmacokinetic models to simultaneously describe
14 this relationship between concentrations and
15 therapeutic response. Using linked models of
16 pharmacokinetics with either fever reduction data
17 or pain relief data, estimates of EC50 have been
18 obtained for acetaminophen. Mean estimates of EC50
19 for acetaminophen in children with fever from 10 to
20 7 micrograms per mil appear to be slightly lower
21 than the EC50 of 10 micrograms per mil reported for
22 pain relief following tonsillectomy.

1 In adults, mean EC50 for pain relief ranged
2 from 9.4 to 16.6 micrograms per ml following dental
3 surgery. Because there were no reported estimates
4 of EC50 in children from 6 to 23 months, McNeil
5 recently completed a linked
6 pharmacokinetic/pharmacodynamic analysis in this
7 age group.

8 Pediatric data for 82 children were
9 available for McNeil fever studies for modeling.
10 This slide includes example results for two
11 children who had received the 10 to 15 milligram
12 per kilo dose at time zero and again at four hours.

13 The figure on the left includes plasma
14 acetaminophen concentrations for a 7 and a half
15 month-old male and, on the right, for a 5-year-old
16 female. When each child's temperature data are
17 overlaid on the same figure, we see that the
18 response curves show a double dip corresponding to
19 the two administered doses. Pharmacokinetic and
20 pharmacodynamic data for the remaining children
21 were modeled and estimates of EC50 were obtained.

22 Here, results for individual EC50 estimates

1 are summarized as box plots by age group, with the
2 center line as the median and the 25th and 75th
3 percentiles as top and bottom. These data indicate
4 that the response to acetaminophen by children 6 to
5 23 months and 2 to 11 years was comparable. This
6 is not surprising because it's reasonable to
7 presume that physiological processes associated
8 with fever and normal temperature controls is
9 similar in children from 6 months through 11 years
10 of age.

11 In summary, the 10 to 15 milligram per kilo
12 OTC dose is appropriate for children 6 to
13 23 months, because it provides similar
14 acetaminophen exposure as children 2 to 11 years.
15 The relationship between acetaminophen
16 concentrations and fever reduction is the same for
17 both pediatric groups, suggesting similar drug and
18 physiological responses. Although there are
19 adequate fever data in this age group, results of
20 these analyses in children 6 to 23 months provide a
21 reasonable bridge to efficacy data in children 2 to
22 11 years as the reference group.

1 Thank you for your attention. And next,
2 Dr. Kuffner will speak about pediatric efficacy and
3 safety data.

4 **Industry Presentation - Ed Kuffner**

5 DR. KUFFNER: Good afternoon. I'm Ed
6 Kuffner. I'm the Vice President of Medical Affairs
7 and Clinical Research at McNeil Consumer
8 Healthcare. As an emergency physician, I've
9 treated many children with acetaminophen, children
10 who have had pain, children who have had fever.

11 When my three children were under 2 years of
12 age, my wife frequently asked me how much
13 acetaminophen she needed to give our kids, because
14 she couldn't find the dose on the over-the-counter
15 label. My children now are 4, 8 and 10, and so my
16 acetaminophen dosing services are no longer needed
17 within our household, but I continue to be called
18 by family and friends to provide directions for
19 acetaminophen dosing for their young children.

20 I know that most health care providers, as
21 well as those on this committee, have had similar
22 experiences. As a toxicologist, I believe that the

1 lack of dosing information on the over-the-counter
2 label for children 6 to 23 months of age has not
3 only contributed to medication errors like we heard
4 this morning, but also has contributed to
5 acetaminophen overdose.

6 Dr. Gelotte answered the first part of
7 question number 2 related to the pharmacokinetics.
8 First, I'd like to review antipyretic efficacy data
9 in children 6 to 23 months of age; then I'll review
10 analgesic efficacy data, and, finally,
11 acetaminophen safety data.

12 Adding specific dosing information to the
13 over-the-counter label for children 6 to 23 months
14 of age is supported by both efficacy, as well as
15 safety data. McNeil agrees with FDA's conclusions
16 from the published studies that were outlined in
17 the briefing materials, as well as outlined in the
18 presentations this morning, that there is
19 significant data in the published trials of
20 antipyretic efficacy.

21 In addition to these data, McNeil has
22 conducted multiple antipyretic efficacy trials in

1 younger and older children. These support the
2 antipyretic efficacy of acetaminophen at the 10 to
3 15 milligram per kilogram dose.

4 As described in our briefing book, we
5 identified 13 McNeil studies conducted since 1980
6 that included one or more oral acetaminophen
7 treatment arms and evaluated the 10 to 15 milligram
8 per kilogram dose for the treatment of fever in
9 children. Four of these studies enrolled children
10 that were under 2 years of age, as well as over 2
11 year of age, and these studies allowed us to
12 compare the antipyretic effects of children 6 to
13 23 months compared to children 2 to 11 years of
14 age.

15 This figure shows the mean change from
16 baseline for these four studies. On the vertical
17 axis, you see the mean temperature decrement in
18 degrees Celsius, and, on the horizontal axis, you
19 see the time in hours following acetaminophen
20 dosing. So, remember, a change of 1 degree Celsius
21 is equal to a change of about 1.8 degrees
22 Fahrenheit.

1 The mean temperature from baseline and the
2 95 percent confidence intervals are shown for the
3 two groups, children 6 to 23 months by the solid
4 yellow line and children 2 to 11 years by the
5 dashed blue line. When dosed by weight using
6 schedules to achieve doses in the 10 to
7 15 milligram per kilogram range, the antipyretic
8 response is very similar between children 6 to
9 23 months and children 2 to 11 years. The
10 pharmacokinetics and the pharmacodynamics of
11 acetaminophen are similar in younger children and
12 older children.

13 Turning now to the question of analgesic
14 efficacy. We agree with FDA that there are few
15 studies in children less than 2 years of age for
16 this specific indication. This reflects challenges
17 in conducting and interpreting pain trials in young
18 children, like you heard this morning.

19 I'll present data from two placebo-
20 controlled studies that enrolled children 6 to
21 23 months of age and included analgesic endpoints.
22 These studies provide additional evidence of the

1 analgesic efficacy of acetaminophen in young
2 children.

3 There was a study by Ipp and colleagues
4 which supports the analgesic efficacy of
5 acetaminophen in children less than 2 years of age.
6 This was a randomized, double-blind, placebo-
7 controlled study of children 2, 4, 6, and 18 months
8 of age receiving DPT plus polio vaccination. Five
9 hundred and nineteen vaccination episodes in 452
10 children were evaluated. Children were randomized
11 to receive acetaminophen 15 milligrams per kilogram
12 or placebo immediately following vaccination and
13 every four hours for two doses and then every four
14 hours as needed. Parents evaluated multiple
15 endpoints, including local injection site pain.
16 The parents used a four-point categorical scale,
17 none, mild, moderate, and severe to assess that
18 injection site pain.

19 On the vertical axis, you see the percent of
20 parents reporting moderate to severe pain for
21 acetaminophen-treated children and those receiving
22 placebo. As reported in the paper, for children 2,

1 4 and 6 months, moderate to severe pain at the
2 injection site was reported in 31.5 percent of
3 children receiving placebo and 16.3 percent of
4 children receiving acetaminophen, and this
5 difference was statistically significant. Symptoms
6 such as fretfulness and crying, which in and of
7 themselves may be markers of pain in young
8 children, were also statistically different in the
9 acetaminophen group compared to the placebo group.

10 So these results suggest that acetaminophen
11 does produce analgesia in children less than
12 2 years of age.

13 There was another study that's quite similar
14 to this one, and this was conducted by Lewis and
15 colleagues, and this also supports the analgesic
16 efficacy of acetaminophen in children less than
17 2 years of age. This was a randomized, double-
18 blind, placebo-controlled study and included
19 children 2, 4, 6, or 18 months of age, as well as 4
20 to 6-year-old children receiving DPT vaccination.

21 Two hundred and eighty-two children were
22 enrolled in this study; 145 received age-related

1 dosing of acetaminophen targeted to the 10 to
2 15 milligram per kilogram range, and 136 of these
3 children were less than 2 years of age; 137
4 received placebo.

5 In this study, the medications were
6 administered 30 minutes prior to vaccination and
7 then 3, 7, 12 and 18 hours post-vaccination. And,
8 again, in this study, the parents evaluated their
9 child's pain using a four-point categorical pain
10 scale. Acetaminophen-treated children experienced
11 significantly less pain compared to placebo-treated
12 children. The mean pain severity score was 0.94 in
13 the acetaminophen group and 1.32 in the placebo
14 group.

15 Subjective assessments of pain by children
16 younger than 2 years of age are unreliable. We
17 heard that this morning. But there is a study by
18 Schachtel that was published in 1993 that
19 demonstrates the analgesic efficacy of
20 acetaminophen in older children with sore throat
21 pain.

22 This was a randomized, double-blind,

1 placebo-controlled, single-dose study of
2 acetaminophen 15 milligrams per kilogram, ibuprofen
3 10 milligrams per kilogram, as well as placebo. In
4 this study, children 3 and a half to 12 and a half
5 years old with at least moderate sore throat pain
6 from an upper respiratory infection were enrolled.

7 In this study, the children rated their pain
8 intensity. They used an age-appropriate visual
9 analog scale and pain relief with a smiley face
10 scale. And parents and pediatricians, as well,
11 they rated pain using a visual analog scale and a
12 five-point categorical scale.

13 Now, on this slide, you see the children's
14 assessments for each of the two age-appropriate
15 scales. On the vertical axis, you see the mean
16 pain intensity difference; and, on the horizontal
17 axis, you see the time following dosing.

18 Acetaminophen is represented by the blue lines,
19 ibuprofen by the pink lines, and placebo by the
20 white lines.

21 On the left side, you see the results using
22 a visual analog scale, and on the right side, those

1 using the smiley face scale. Both scales show a
2 statistically significant reduction in pain between
3 acetaminophen and placebo. And as expected,
4 acetaminophen had an earlier onset of pain relief
5 and ibuprofen had a longer duration of analgesia.

6 It's also important to consider how
7 acetaminophen is being used in children less than
8 2 years of age. We heard some talk about this,
9 this morning. We know that pediatricians commonly
10 recommend acetaminophen for pain. In children less
11 than 2 years of age, pediatricians recommend
12 acetaminophen more than any other analgesic.
13 Common indications include otitis media, sore
14 throat, teething, and minor traumatic conditions.

15 As Dr. Gelotte presented, the PK data
16 demonstrate that the concentration time profiles
17 for children 6 to 23 months are consistent with
18 those 2 to 11 years of age. They're also
19 consistent with adults. PK data demonstrate that
20 acetaminophen exposures following the 10 to 15
21 milligram per kilogram dosing are comparable for
22 children 6 to 23 months and those 2 to 11 years of

1 age.

2 Data from our own internal McNeil
3 antipyretic trials demonstrate that when
4 acetaminophen is dosed by weight, the antipyretic
5 response is very similar between the younger
6 children in the 6 to 23-month-old age group
7 compared to children 2 to 11 years of age.

8 Published data also demonstrate that
9 acetaminophen is an effective analgesic in children
10 less than 2 years of age. And in those children
11 who were old enough to reliably self-report with
12 the relief of sore throat pain, acetaminophen was
13 significantly better than placebo.

14 Given acetaminophen's extensive history of
15 use as an analgesic in children less than 2 years
16 of age in both clinical practice and in real world
17 settings, it's certainly appropriate to provide an
18 analgesic indication in addition to the antipyretic
19 indication on the over-the-counter label for
20 children 6 to 23 months of age.

21 I'd like to switch gears a little bit here
22 and talk about the safety of acetaminophen in

1 children 6 to 23 months of age. There is a
2 considerable body of published and McNeil clinical
3 trial data and over 50 years of clinical use that
4 support the safety of acetaminophen both at single
5 and multiple doses of 10 to 15 milligrams per
6 kilogram.

7 The table here outlines high level details
8 from McNeil unpublished trials, the Boston
9 University Fever Study, and other published trials.
10 We've individually listed the Boston University
11 Fever Study as it was one of the largest pediatric
12 trials ever conducted, and it was also supported by
13 McNeil Consumer Healthcare.

14 In the second column, you see the number of
15 trials. In the third column, you see the number of
16 children treated with acetaminophen; and, in the
17 last column, the number of children less than
18 2 years of age. As you heard this morning, in most
19 of the published trials, the age ranges were
20 provided, but not the ages of individual
21 participants. So, therefore, in most of the
22 published trials, it's not possible to determine

1 the exact number of children less than 2 years of
2 age. We did confirm that in over 13,000 children
3 treated with acetaminophen in these published
4 trials, there were over 500 children less than
5 2 years of age.

6 In the Boston University Fever Study, more
7 than 28,000 children were treated with
8 acetaminophen, of which over 9,000 were children
9 less than 2 years of age. Across all these
10 studies, acetaminophen was well tolerated. It was
11 well tolerated in the McNeil and the published
12 trials. As expected with any oral medication, the
13 most common adverse events were gastrointestinal in
14 nature. You saw that this morning, things like
15 nausea, vomiting, as well as abdominal pain.

16 In the McNeil studies, there were no serious
17 adverse events in any of the acetaminophen-treated
18 children. In the 71 published trials that included
19 over 13,000 children, serious adverse events were
20 rare. There were four serious adverse events that
21 were reported, and you see those listed on the
22 slide.

1 I'd now like to discuss the Boston
2 University Fever Study. This was a large, multi-
3 dose safety study that really confirmed the safety
4 of acetaminophen in children less than 2 years of
5 age. This was a randomized, double-blind,
6 pragmatic safety study that was conducted in
7 multiple physicians' offices, pediatricians, family
8 physicians, and general practitioners. Over 84,000
9 children, 6 months to 12 years of age, with an
10 acute febrile illness were included.

11 Acetaminophen in this study was dosed by
12 weight at 12 milligrams per kilogram, and there
13 were two different weight-based ibuprofen arms.
14 Dosing instructions allowed the caregivers to
15 repeat doses every four to six hours to a maximum
16 of five doses per day.

17 Over the course of the study, children
18 received six to 10 doses of medication over this
19 three-day treatment period. The main outcome
20 measure in this study was caregiver-reported
21 serious adverse events resulting in
22 hospitalization.

1 The researchers also attempted to identify
2 unrecognized serious reactions. On this slide, you
3 see selected discharge diagnoses judged to be
4 possibly drug-induced. The absolute number of
5 children and the risk per 100,000 children treated
6 is listed for both acetaminophen, as well as
7 ibuprofen. Based upon the results of this study,
8 the risk for any of these adverse events are very
9 rare.

10 Of the 28,130 children in the Boston
11 University Fever Study treated with acetaminophen,
12 9,127 were children less than 2 years of age.
13 There was one death in an acetaminophen-treated
14 child secondary to a motor vehicle accident. No
15 acetaminophen-treated child had a serious adverse
16 event that was hepatic in nature. The absolute
17 risk of hospitalization for any reason was 1.4
18 percent with acetaminophen.

19 This large safety study confirms the safety
20 of acetaminophen when dosed at 10 to 15 milligrams
21 per kilogram in children less than 2 years of age.
22 Data from the Boston University Fever Study,

1 coupled with the safety data from clinical trials
2 and extensive real world use, support adding dosing
3 information to the over-the-counter label for
4 children 6 to 23 months of age.

5 I'd like to switch gears again here and
6 really address FDA's first question regarding
7 weight-based dosing for children 2 to 11 years,
8 and, in addition, I'd like to discuss the merits of
9 weight-based dosing for children 6 to 23 months of
10 age.

11 So weight-based dosing, in addition to age-
12 related dosing, for children to 2 to 11 years of
13 age has been on over-the-counter labels for single-
14 ingredient acetaminophen-containing medicines for
15 almost 30 years. The directions section of the
16 over-the-counter label for children's acetaminophen
17 includes a dosing chart, and there was some
18 discussion this morning about dosing charts. Let's
19 focus on that dosing chart for a minute here.

20 In the first column, you have weight ranges
21 in pounds for weight-based dosing. The weight
22 ranges increase by 12-pound increments. As you see

1 on the slide, in the second column, you have age
2 ranges in years for age-related dosing. And in the
3 third column, you have the dose in both milliliters
4 and teaspoons. Now, on the OTC label, the dose
5 isn't represented in milligrams, but we did put it
6 on the chart that I'll show you later. But the
7 dose increases by 80 milligram increments on this
8 chart.

9 Caregivers are encourage to dose by weight.
10 The directions include a statement, "Find right
11 dose on chart below. If possible, use weight to
12 dose; otherwise, use age."

13 This is a graphical representation of the
14 current weight-based dosing schedule for
15 acetaminophen. I'm going to show you a number of
16 slides like this, and I just want to walk you
17 through the setup of these slides.

18 So on the vertical axis, you see the dose in
19 milligrams per kilogram. On the horizontal axis,
20 you see the weight in pounds. The vertical yellow
21 lines across the horizontal axis delineate the 12-
22 pound weight breaks. Across the top you see the

1 dose for each weight range in milliliters,
2 teaspoons, and now it's shown in milligrams.

3 Doses increase by 80 milligram increments,
4 giving you a five-cut dosing chart. The light blue
5 shading represents the 10 to 15 milligram per
6 kilogram range. Weight-based dosing, by design,
7 maintains the dose within this range for all
8 weights. This really is the advantage of weight-
9 based dosing.

10 Although weight-based dosing provides more
11 consistent dosing between 10 to 15 milligrams per
12 kilogram, it's also important to have age-related
13 dosing on the over-the-counter label. It's needed
14 because there are some caregivers who don't know
15 their child's weight.

16 The age-related schedule was created by
17 matching the same incremental dosing increases used
18 for the weight-based schedule to maintain the dose
19 for average weight children within the 10 to 15
20 milligram per kilogram range.

21 Current CDC growth charts were used to
22 determine the average weights for different

1 percentiles. The weight for age ranges were
2 calculated using the 10th percentile weight for age
3 for the youngest age in the range and the 90th
4 percentile weight for age for the oldest age in the
5 range.

6 It's important to understand that separate
7 approaches were used to create the age-related
8 dosing chart and the weight-based dosing chart, and
9 this explains why age and weight may not always
10 match in the dosing chart for some children,
11 especially those children who are at the extremes
12 of weight for age.

13 Let's walk through an example of how the
14 age-related schedule was constructed for a 5-year-
15 old. Although the average for boys and girls was
16 used to calculate the weights, I'm only going to
17 show you the data for boys; it makes it a little
18 bit simpler.

19 The 50th percentile weight for a 5-year-old
20 boy is 18.4 kilograms, and it's shown with the blue
21 dot. The 10th percentile is 15.8 kilograms, and
22 it's shown with the yellow dot. And the 90th

1 percentile is 22 kilograms, and shown with the pink
2 dot.

3 This is a graphical representation of age-
4 related dosing schedule that's currently on the
5 over-the-counter label for children's
6 acetaminophen. Similar to what I showed you, on
7 the vertical axis you see the dose in milligrams
8 per kilogram. The yellow line shows the 10th
9 percentile for weight. The blue lines with the
10 dots show the 50th percentile, and the pink lines
11 show the 90th. Since children in the 10th
12 percentile are smaller, their milligram per
13 kilogram dose is greater and they appear above the
14 50th percentile.

15 On the horizontal axis, you see the age in
16 years, and the age breaks listed across the
17 horizontal axis correspond to the age ranges in the
18 dosing chart. As you can see, age-related dosing
19 for the 50th percentile weight for age children is
20 maintained within the 10 to 15 milligram per
21 kilogram range. Age-related dosing for children
22 who are the extremes of weight for age are near the

1 target range. Both age-related and weight-based
2 dosing provide an appropriate dose, but when
3 possible, dosing by weight is preferred.

4 The weight-based schedules and current age-
5 related dosing schedules linked by these five
6 80 milligram incremental increases in dose from
7 160 milligrams to 480 milligrams is appropriate for
8 the over-the-counter label for children 2 to
9 11 years. This weight-based and age-related dosing
10 schedule, it's been on the OTC label since the
11 early 1980s. Caregivers, health care providers,
12 they're both familiar with this dosing schedule,
13 and this schedule should be officially adopted as
14 part of the over-the-counter monograph.

15 You can use a similar approach to develop
16 weight-based and age-related dosing schedule for
17 children 6 to 23 months, and I'd like to take you
18 through that, as well. For decades, manufacturers
19 have voluntarily provided health care providers
20 with weight-based and age-related dosing for
21 children less than 2 years of age. These schedules
22 continue to be requested by and made available to

1 health care providers. Since all manufacturers, as
2 you heard this morning, are moving to a single
3 concentration of pediatric acetaminophen liquids,
4 we use this new concentration to illustrate how
5 weight-based and age-related dosing would appear on
6 the over-the-counter label.

7 This is our recommended label for children 6
8 to 23 months and 12 to 23 pounds. It has both
9 weight-based and age-related dosing on it in a
10 format that's similar to the current label for
11 older children and similar to the current format
12 that's used currently on the infant's
13 acetaminophen-containing products.

14 The dosing chart has the volumes for the new
15 single concentration, and this chart has two
16 different doses and, as such, is referred to as a
17 two-cut dosing chart. So the dosing cut for the
18 older children was a five cut; this is a two-cut
19 dosing chart.

20 Similarly, on this label, caregivers would
21 be encouraged to dose by weight and the directions
22 section would include a similar statement, "Find

1 right dose on chart. If possible, use weight to
2 dose; otherwise, use age." This recommended over-
3 the-counter label is similar to that which is
4 currently provided to health care providers, and
5 health care providers have been recommending these
6 same milligram doses to children from 6 to
7 23 months for almost 30 years. So this isn't
8 something new.

9 This is a graphical representation of
10 weight-based dosing for children 6 to 23 months.
11 The weight-base schedule for these younger children
12 uses two 6-pound increments, 12 to 17 pounds and 18
13 to 23 pounds; a dose of 80 milligrams for children
14 12 to 17 pounds and a dose of 120 milligrams for
15 children 18 to 23 pounds. As you saw with the
16 older children, weight-based dosing always
17 maintains the dose within the blue shaded range of
18 10 to 15 milligrams per kilogram.

19 Ibuprofen medicines have had dosing for
20 children 6 to 23 months on the over-the-counter
21 label for over 10 years. The proposed weight
22 ranges and age ranges for acetaminophen, they'd be

1 identical to those that are current on the over-
2 the-counter label for ibuprofen.

3 This is a graph for the age-related dosing
4 schedule for children 6 to 23 months. And, again,
5 as you saw with the older children, the age-related
6 dosing schedule maintains the dose near the 10 to
7 15 milligram per kilogram target range.

8 So, in summary, it's important to have both
9 weight-based and age-related dosing on the over-
10 the-counter label. Both schedules provide an
11 appropriate dose. Weight-based dosing maintains
12 the dose within the 10 to 15 milligram per kilogram
13 range for all of the children. And it's important
14 to have age-related dosing on the schedule, because
15 there are some caregivers who don't know their
16 child's weights.

17 The time has come to officially amend the
18 over-the-counter monograph to include weight-based
19 dosing for children from 2 to 11 years as it's
20 provided today on the over-the-counter label of
21 children's acetaminophen-containing medicines.
22 It's also important to include weight-based and

1 age-related dosing on the over-the-counter label
2 for children 6 to 23 months of age.

3 Adding dosing information to the over-the-
4 counter label for children 6 to 23 months, there's
5 no question in my mind, it's going to decrease
6 medication errors, and it will decrease
7 acetaminophen overdose. With the support of this
8 committee, I hope FDA will act with alacrity so
9 that we can add important dosing information to the
10 over-the-counter label.

11 I'd like to end by addressing some of the
12 information that I think will be helpful for you to
13 answer the question number 4.

14 The data from real world use demonstrate
15 that a single strength of children's chewables is
16 not warranted. Currently, there are two strengths
17 of children's chewables. The 80 milligram strength
18 has been on the market since 1972, and the 160
19 milligram strength for children 6 to 11 years was
20 introduced in 1990. The 160 milligram strength
21 limits the number of tablets that an older child
22 needs to take.

1 If we only have the 80 milligram strength,
2 as you see on the slide, an 11-year-old child would
3 need to take six tablets instead of three, and this
4 is certainly not the type of dosing behavior we
5 want to instill in our children, especially at an
6 age when many are starting to self-medicate.

7 As you see on this slide, and it was
8 discussed this morning, you see the percentage of
9 dosage units sold for the different forms of
10 single-ingredient pediatric acetaminophen
11 medicines. On the vertical axis, you see the
12 percentage of dosage units; and, on the horizontal
13 axis, you see the different forms. Liquids account
14 for about 74 percent and the chewable tablets
15 account for about 26 percent of all pediatric
16 dosage units sold.

17 The number for the McNeil Consumer Care
18 Center, it's listed on the label of all of our
19 Tylenol medicines. Caregivers call us and ask us
20 questions, health care providers call us and ask us
21 questions.

22 We went back and looked at two years' worth

1 of data. In 2008 and 2009, there were more than
2 73,000 phone calls regarding infant's and
3 children's Tylenol products. Of these, 3.8 percent
4 or 2,792 calls related to the 80 milligram and 160
5 milligram chewable tablets.

6 Over this entire two-year period, four
7 callers specifically asked about the difference
8 between the two strengths of children's chewables.
9 From this data, it's clear that caregivers have
10 very few questions about the difference between the
11 80 milligram and the 160 milligram strengths.

12 On top of that, we wanted to go back and
13 look at adverse event data. So we reviewed seven
14 years of McNeil's postmarketing data looking for
15 medication errors related to confusion between the
16 80 milligram and the 160 milligram strengths.

17 We looked at reports from the United States
18 that were coded with a preferred term suggestive
19 that a potential medication error may have been
20 made. Three reports over these seven years
21 mentioned confusion between the 80 milligram and
22 the 160 milligram strengths, and in these three

1 reports, there were no clinical adverse events that
2 were reported.

3 So restricting the oral solid dosage forms
4 to a single strength based upon the data is not
5 warranted. And there's an important reason why
6 there's a difference between the liquid
7 concentrated products and the solid dose forms
8 here. The presence and absence of dosing
9 information on the over-the-counter label, that's
10 the critical difference between the solid and the
11 liquid formulations.

12 Importantly, there is dosing information on
13 the over-the-counter label for both the
14 80 milligram and the 160 milligram solid dose
15 strengths. But specific doses, as we've heard
16 talked about this morning, when it comes to
17 medication errors, acetaminophen overdose, they're
18 not on the over-the-counter label for children less
19 than 2 years of age. And not having specific
20 dosing on the over-the-counter label for those
21 children who are most likely to be using the
22 medicine, that's the root cause of medication

1 errors and that's unique to children less than 2.

2 If we only had the 80 milligram strength,
3 older children, as I said earlier, would need to
4 take up to six tablets, and I don't think that's
5 the type of dosing behavior I want to encourage for
6 my kids or any of you want to encourage for your
7 patients or your children. We also don't want
8 people, if you only had the 160 milligram strength,
9 needing to split more scored tablets. So in my
10 opinion and based upon the data, the data don't
11 support moving to one strength of pediatric
12 chewables.

13 I know it's a long presentation. I
14 appreciate your attention. And I'd like to ask
15 Dr. Randall Bond to come up and discuss his
16 perspectives on the use of acetaminophen in
17 children.

18 **Industry Presentation - Randall Bond**

19 DR. BOND: Good afternoon. Thank you for
20 the opportunity to speak to you today. In terms of
21 disclosure, CHPA is compensating me for my time and
22 my expenses to be here, but I'm excited to speak to

1 you today because I think the interests of
2 patients, the results of my own research, the plans
3 of industry, and the recommendations of the FDA are
4 in alignment.

5 I'm here today as a pediatrician, poison
6 center medical director, researcher, and author of
7 several papers on acetaminophen-related injuries in
8 children. In addition to my work as a poison
9 center medical director, I see children every week
10 in the pediatric emergency department at Cincinnati
11 Children's Hospital.

12 Because of my varied experience, I
13 appreciate both the therapeutic value of
14 acetaminophen to children and the risks associated
15 with its incorrect use. I'm encouraged by what
16 I've heard, that we are now considering
17 improvements to the label to make it easier for
18 parents to administer the proper dose, and
19 especially that industry is moving to a single
20 concentration of pediatric oral medicines. Both of
21 these address root causes identified in my own
22 research. I'm also reassured by the fact that

1 there is a continuing focus on educating parents
2 and caregivers on the appropriate use and storage
3 of these medicines.

4 In the next few minutes, I want to provide
5 some perspective on what pediatricians are already
6 doing about dosing in this age group and on
7 recommendations for curbing the injuries associated
8 with acetaminophen.

9 The American Academy of Pediatrics supports
10 weight-based dosing of acetaminophen and the
11 addition of dosing on the label for children under
12 2 years of age. Over the years, the AAP has
13 repeatedly address the use of acetaminophen. In
14 its clinical report on fever and antipyretic use in
15 children, released just this year, the AAP's
16 Committee on Drugs again stated acetaminophen doses
17 of 10 to 15 milligrams per kilogram per dose given
18 every four to six hours orally are generally
19 regarded as safe and effective.

20 Providing dosing instructions is not new to
21 the academy. Recognizing that most acetaminophen
22 therapy is begun without direct advice from a

1 pediatrician, since 2001, the academy has
2 recommended that pediatricians provide dosing
3 instructions to parents before the occurrence of a
4 fever at well child visits.

5 More recently, in its parent education book
6 and on its website for parents, the academy has
7 provided parents with a weight-based dosing chart.
8 It specifically states age is provided as a
9 convenience only. In fact, this chart, which is on
10 the website and in the book, is almost identical
11 with the weight-based chart that McNeil has
12 recommended. The only difference is that the AAP
13 provides dosing for under six months and McNeil is
14 still recommending that parents call a doctor for
15 dosing in this age group.

16 Improving the label with these dosing
17 instructions also makes acetaminophen labeling
18 parallel to ibuprofen. Right now, ibuprofen, the
19 other main treatment for fever and pain, has both
20 weight-based labeling and labeling for children
21 down to 6 months of age. Making the labels for
22 these two treatments for children's fever and pain

1 consistent would further reduce confusion.

2 Let me also briefly address acetaminophen
3 use for pain in children under 2 years of age.
4 Despite the limitation of previous studies in this
5 age group, the American Academy of Pediatrics, the
6 American Pain Society, and the American Academy of
7 Family Physicians all recommend the use of
8 acetaminophen as a treatment option for pain
9 associated with illnesses, such as sore throat and
10 earache, in all age groups. These recommendations
11 are consistent with both parent and hospital
12 practice. I've practiced in five cities. In all
13 of them, acetaminophen has been used for these
14 types of pain in children that are very young. In
15 pediatric emergency departments -- I'm sorry. In
16 the pediatric emergency department at Cincinnati
17 Children's Hospital, we assess pain at triage in
18 all patients and we give acetaminophen as our first
19 line treatment for fever and minor pain.

20 Now, I'd like to talk about the sources of
21 acetaminophen-related injuries and interventions
22 that I believe are needed to address them.

1 Data from the CDC show that 97 percent of
2 acetaminophen-related emergency department visits
3 by children up to 5 years of age come from
4 unsupervised ingestions, children getting into
5 these medicines on their own and ingesting a
6 potentially large amount. The remaining 3 percent
7 are from therapeutic errors.

8 While unsupervised ingestions account for
9 the overwhelming majority of emergency department
10 visits, it's important to note that half of all
11 serious pediatric injuries related to acetaminophen
12 come from the 3 percent of cases involving
13 therapeutic errors.

14 I'd like to take a minute to look more
15 closely at the root causes of therapeutic errors.
16 Specifically, I'd like to take a moment to discuss
17 a large therapeutic errors study my colleague, Lee
18 Tzimenatos and I performed, with the help of all 61
19 U.S. poison centers. This research supports the
20 need for many of the recommendations under
21 discussion today.

22 We queried the electronic database of the

1 American Association of Poison Control Centers,
2 what you've heard earlier today as NPDS, from 2000
3 through 2004 for all cases of serious outcome after
4 therapeutic error in children 5 years of age and
5 younger. And then to get at the root cause, we
6 contacted each poison center for the case details.
7 We were particularly interested in cases where the
8 errors occurred at home. In this five-year period,
9 25 of the 162 serious injuries and deaths from
10 therapeutic errors that occurred at home involved
11 acetaminophen. All 25 involved liver injury.

12 Let's look more closely at the majority of
13 severe cases, particularly those involving children
14 under 2. In the highlighted column, we see that 13
15 of the 25 injuries occurred in children under 2
16 years of age. When we looked more closely at the
17 scenarios and root causes of the excessive doses,
18 we found that confusion between pediatric
19 formulations was the most common error, involving
20 eight of 25 children, almost a third.

21 It was especially the case in those under
22 2 years of age; 6 of 13, almost half, were victims

1 of formulation substitution error. Movement to a
2 single concentration alone could have prevented six
3 serious injuries and two deaths in this five-year
4 period.

5 Looking at the next line, in seven cases, an
6 excessive dose was administered, but the reason
7 wasn't clear from the case notes. Five of the
8 seven children were under 2 years of age. What is
9 clear from the data is the confusion over what to
10 dose and how much to dose, especially in young
11 children, is responsible for most of these rare,
12 but serious cases. The good news is that the
13 proposals under discussion today directly address
14 these issues.

15 In conclusion and on the basis of the data I
16 have reviewed and what we know the medical
17 community is already doing and endorsing, I fully
18 support what is being recommended today by the FDA
19 and CHPA. As I said, 97 percent of acetaminophen-
20 related ED visits and half of the serious injuries
21 result from unsupervised ingestions. We should all
22 be educating parents and caregivers that all

1 medicines, OTC and prescription, must be stored in
2 a safe place out of reach and out of sight of
3 children every time they're used. Parents must
4 also be reminded that they need to put the child-
5 resistant safety caps back on after every use.

6 But education has not been enough. I
7 believe with the FDA, in their statements this
8 morning, that safety packaging must be improved.
9 This should include improvements in child-resistant
10 closures and barriers to limit the amount of
11 medicine children can easily get if they're able to
12 remove the cap.

13 In addition, I'd like to see us take
14 concrete action to reduce therapeutic errors with
15 acetaminophen. Moving to one liquid concentration
16 is great, but it's not enough. To prevent
17 uncertainty and guesswork in dosing, I'd like to
18 see the dosing instructions on the label of OTC
19 pediatric acetaminophen products start at 6 months
20 of age. These instructions should match the
21 instructions that pediatricians are already giving
22 out to parents, and they should be accessible to

1 parents where and when they're needed. I support
2 the AAP's choice to dose preferentially by weight
3 and secondarily by age, and I believe the dosing
4 directions on the label should be consistent with
5 that.

6 I urge the committee and the FDA to take
7 these steps and help us make these medicines safer
8 for children. Thank you for your time and
9 attention. Thank you, again.

10 **Industry Presentation (continued)**

11 **Barbara Kochanowski**

12 DR. KOCHANOWSKI: Thank you, Dr. Bond.

13 We believe we have presented practical and
14 effective actions to further improve the safe use
15 of these products. Importantly, our actions are
16 aligned with what the FDA has been recommending.

17 One of our most important efforts is
18 education. We're partnering with an impressive
19 group of agencies and associations to educate
20 health care providers, parents, and caregivers to
21 safely use our medicines. These programs are
22 research-based, focused on the issues you heard

1 today and are designed to achieve specific goals.
2 Let me take you through some of the details of our
3 programs.

4 Two of our most important initiatives are
5 the No Your Dose campaign and the CDC PROTECT
6 Initiative. Each has a specific audience and
7 targeted messages, and we will use a variety of
8 channels to ensure we are reaching the right
9 audience at the right time.

10 The Know Your Dose campaign, which is aimed
11 at health care providers, begins next month as a
12 project of the Acetaminophen Awareness Coalition.
13 The coalition, formed in 2009, consists of a wide
14 range of diverse stakeholders, including the
15 American Pharmacists Association, the National
16 Consumers League, and many other important groups.
17 The FDA, the CDC, and the American Academy of
18 Pediatrics are advisors to this group, and Know
19 Your Dose is also part of FDA's Safe Use
20 Initiative.

21 The purpose of the coalition and its
22 campaign is to raise awareness about the dangers

1 and consequences of taking too much acetaminophen.
2 As part of this program, CHPA members sponsored
3 research to understand what messages would be most
4 effective at raising awareness and communicating
5 the consequences of overdose. As a result of the
6 testing, we now have messages that are direct,
7 clear and specific.

8 Know Your Dose is designed to target
9 consumers and patients with educational print
10 materials and videos through trusted health care
11 providers, reaching them when dosing decisions are
12 top of mind, at pharmacies, in-store clinics,
13 doctors' offices, and hospitals. The program has
14 its own website, knowyourdose.org, where both
15 consumers and health care providers can download
16 free educational materials.

17 The coalition is surveying both consumers
18 and health care providers to ensure the program is
19 relevant, and we'll refine it as needed. We
20 captured the baseline awareness of acetaminophen
21 when the program started, and we'll measure the
22 impact the program is having to change awareness.

1 CHPA and our members are also actively
2 involved in the PROTECT initiative with the CDC and
3 other stakeholders to keep children safe from
4 unintentional medicine overdoses. The goal of
5 PROTECT is to develop labeling, packaging and
6 educational approaches to protect children from
7 accidental medicine overdoses. As part of PROTECT,
8 CHPA's board of directors approved voluntary
9 guidelines in November 2009 to standardize dosing
10 using milliliters, abbreviated as you see it on the
11 slide, to make dosing more accurate and consistent
12 for parents. These voluntary guidelines are now
13 industry-wide and include liquid pediatric over-
14 the-counter medicines containing acetaminophen.

15 To make dosing devices easier to use and
16 dosing more accurate, CHPA members have eliminated
17 extraneous markings on dosing devices and include
18 dosing devices with every OTC pediatric liquid
19 product, in an effort to dissuade parents from
20 using less accurate household spoons.

21 In addition to improving dosing and dosing
22 devices, the PROTECT initiative also includes an

1 education campaign. The Up and Away and Out of
2 Sight campaign was developed to focus specifically
3 on the primary cause of medicine-related emergency
4 department visits among children; that is,
5 unsupervised medicine ingestions.

6 Up and Away and Out of Sight research found
7 that while parents and caregivers know that safe
8 medicine storage is important, they are busy. They
9 need and welcome reminders.

10 In addition, the research found that parents
11 do not differentiate where they store their
12 medicines by their perceived potency, but by how
13 often they use them. As a result, they store the
14 medicines they use more frequently in places they
15 will see in order to remember to take them. With
16 this in mind, we refined our key messages to be
17 simple, specific, and practical to follow.

18 The PROTECT partners have approved our
19 content, which includes broadcast and public
20 service announcements, pamphlets, and an office
21 poster for health care providers.

22 This is an example of a public service

1 announcement that ran in Parade Magazine. It asks
2 people to spot the medicine before your 2-year-old
3 does, and it's there on the counter inside the red
4 circle. With the support of our partner
5 organizations to multiply these messages, we're
6 confident that this program will have impact.

7 In summary, acetaminophen is used
8 extensively and very safely in children, and today
9 we have outlined our plan to ensure that parents
10 and caregivers will be able to use these products
11 even more safely. As I conclude, I'd like to
12 reiterate both what we are recommending and what we
13 have already done.

14 First, we strongly support adding dosing
15 directions for children 6 months to under 2 years
16 to the OTC label; requiring weight-based dosing for
17 children 2 to under 12 years and adding it for
18 children 6 months to under 2 years; and, keeping
19 age-related directions on the label.

20 In addition, our members are moving to one
21 concentration for children's liquids; standardizing
22 dosing devices with consistent and easily visible

1 measurement markings; standardizing the
2 abbreviation for milliliter on dosing charts and
3 devices; improving our packaging to prohibit easy
4 emptying of contents; and, launching additional
5 education programs for consumers and health care
6 providers. Many of these actions and
7 recommendations are consistent with what FDA has
8 highlighted in its briefing materials.

9 Over the past three decades, manufacturers
10 have implemented many voluntary programs to improve
11 the safety of our products. We stand here today
12 united in support of additional measures to improve
13 the safe use of acetaminophen. But we need this
14 committee's support and FDA action to implement two
15 of the most important changes: dosing under 2 and
16 weight-based dosing. We hope that today will be a
17 catalyst for swift action.

18 Thank you for your time and attention, and
19 we look forward to answering your questions.

20 **Clarifying Questions**

21 DR. NEILL: Thank you very much. So we have
22 a period of time available now for clarifying

1 questions from the committee. As with this
2 morning, if you can keep your hands up.

3 Please keep your hands up. And we're going
4 to begin with Dr. Notterman. Keep your hands up,
5 those of you we've not called on yet.

6 [Laughter.]

7 DR. NOTTERMAN: Thank you. Dan Notterman.

8 May I address a question to a specific
9 speaker?

10 DR. KOCHANOWSKI: Certainly.

11 DR. NOTTERMAN: So I guess this is to
12 Dr. Kuffner. Your very lucid presentation
13 convinced me that weight-based dosing improves the
14 calibration of dosage when the dosage is properly
15 administered. But I wonder how adding weight-based
16 dosing to age-based dosing will reduce dosage
17 errors, which are actually the principal cause of
18 life-threatening or serious toxic events.

19 Further, a second part of that question,
20 until consumer studies of understandability are
21 completed, how do we know, in fact, that having two
22 methods of dosing, weight-based and age-based, does

1 not, in fact, confuse some consumers, increasing
2 rather than decreasing the probability of serious
3 overdose? I guess that's my question.

4 DR. KUFFNER: Okay. I don't necessarily
5 believe that adding weight-based dosing to the
6 label is going to decrease medication errors. In
7 order to decrease medication errors, the most
8 important thing is having dosing on the label.

9 What weight-based dosing does do is keep
10 you, as designed, tighter within the 10 to
11 15 milligram per kilogram, and the efficacy studies
12 on acetaminophen and the PK data suggest that that
13 10 to 15 milligram per kilogram does give people
14 adequate efficacy.

15 If people aren't getting adequate efficacy,
16 then certainly there may be a way -- or a reason
17 why that could lead to medication errors in that
18 people may decide to re-dose more frequently than
19 is on the label.

20 DR. NOTTERMAN: Just a quick follow-up. But
21 isn't it possible, unless you have data that you
22 can present regarding the readability and

1 understandability of labels, that having two dosing
2 methods might actually increase the probability of
3 a serious error rather than a minor calibration
4 error, but a serious, potentially life-threatening
5 overdose, such as the kind we heard about in the
6 FDA presentations? That's really my concern.

7 DR. KUFFNER: A number of things. One, what
8 we did was we wanted to understand, if you added
9 weight in addition to age on the label, would that
10 complicate a caregiver's ability to select a
11 correct dose. So we did some consumer research
12 where, with moms of young children, we specifically
13 looked at children from 6 -- moms who had children
14 from 6 to 23 months and actually presented them
15 with a dosing chart that only had age and a dosing
16 chart that had age in addition to weight. And what
17 we found was adding the weight onto the age did not
18 complicate the caregiver's ability to select a
19 correct dose.

20 In addition, this has already been on the
21 label for many years in a similar format. Slide
22 on. And so here what you see is the current dosing

1 chart that's on infant's acetaminophen-containing
2 medicines. It currently has weight in the first
3 column, age in the second, and the doses in the
4 third column. Currently, that label has dosing for
5 children 2 to 3 years in a similar format.

6 What we're asking for is not to change the
7 label, not to have a new label. We're asking just
8 to add the dosing information for children 6 to
9 23 months in a format that's been on the label both
10 for younger children and in a similar format that's
11 been on the label for older children.

12 In addition, we know, even for younger
13 children -- slide on -- that this is how it's been
14 presented for many years. And so here what you see
15 is the current infant's ibuprofen label. And so at
16 McNeil, we manufacture both Tylenol as well as
17 Motrin. What you see is the Motrin label, and that
18 was NDA approved, the infant's form, in 1999. The
19 children's Motrin label has been on the over-the-
20 counter products since 1995.

21 So you heard a little bit of talk earlier
22 this morning about the different regulatory

1 pathways, but the infant's ibuprofen label has been
2 on the market since 1999 in a similar format. And
3 what we're asking for -- and we know that consumers
4 use that, health care providers recommend it. What
5 we're asking for is that the proposed acetaminophen
6 label be identical to, with the same weight cuts
7 and the same age cuts, the two-cut dosing chart, to
8 what's currently available for ibuprofen.

9 DR. NOTTERMAN: Thank you.

10 DR. NEILL: Dr. Goldstein?

11 DR. GOLDSTEIN: My question is for
12 Dr. Kuffner and Dr. Bond. I second the opinion
13 that you all did a very nice presentation, and I
14 think this was very well thought out.

15 My question is that I agree with the
16 direction that you're proposing. One issue that
17 really hasn't been discussed has to do with some of
18 the data that was presented this morning about
19 inappropriate use of crushing adult tablets for use
20 in children, smaller children.

21 So I'm wondering what the current status is
22 and the current thinking is of putting a warning on

1 the adult formulation and on the child formulation
2 that these chewable tablets or the adult tablets
3 should not be used in children.

4 So we're covering most of it, but I don't
5 think we're covering all of it by putting on this
6 additional information on the infant formulation.

7 DR. KUFFNER: So we do know, whether it's in
8 McNeil's postmarketing database, FDA's database,
9 poison center data, that the use of adult medicines
10 in children does lead to overdose. McNeil has for
11 many years and we continue to educate health care
12 providers, as well as caregivers, of the importance
13 of always using a formulation or form that's
14 appropriate for the age range of the child, and we
15 always highlight the importance.

16 In my communications, when "Dear Doctor"
17 letters go out to health care providers, when we,
18 as a company, send information out to caregivers
19 and consumers, we always highlight the importance
20 of not giving adult medicines to children.

21 I think this is something that's critically
22 important. The onus, as we heard this morning, FDA

1 on education, manufacturers on education, and
2 health care providers on education. And I know
3 CHPA, on behalf of all of the companies, actually
4 has education plans around this specific topic.

5 DR. GOLDSTEIN: With all due respect, I
6 think you agreed with me without answering my
7 question.

8 DR. KUFFNER: I think it's totally
9 appropriate that you would have a warning on the
10 adult products not to be used in children. And,
11 again, the labeling for at least the monograph
12 products is controlled by the drug facts labeling
13 by FDA, but the manufacturers would certainly be
14 supportive of that type of labeling.

15 DR. GOLDSTEIN: Thank you.

16 DR. KOCHANOWSKI: Did you also want to hear
17 from Dr. Bond on that?

18 DR. GOLDSTEIN: Only if he disagrees.

19 DR. NEILL: Dr. Walco?

20 DR. WALCO: This is a question for Drs.
21 Gelotte and Kuffner. I want to really zero in on
22 safety, efficacy, and PK data on the 6 to 23-month-

1 olds. So the overwhelming majority of the data you
2 presented were simply comparisons of that age group
3 to subjects who were 24 months and older.

4 I would think there's a pretty fair amount
5 of variability in that younger group. Certainly,
6 6-month-olds have potentially not so much in common
7 with 23-month-olds as compared to 23-month-olds and
8 24-month olds.

9 So have you done analyses within that group
10 to look at differences in PK, safety and efficacy
11 rather than just clump it together and assume that
12 they're a homogenous group? Have you tried to
13 tease out the heterogeneity within that group,
14 especially in the younger end of the spectrum, in
15 terms of safety?

16 DR. KUFFNER: From a safety perspective, we
17 haven't specifically tried to tease out the safety.
18 We know that acetaminophen in real world use has
19 been used -- it's in hospitals. It's been used for
20 children younger than 6 months of age, and the best
21 data that we have is the real world use and then
22 the Boston Fever Study.

1 But we didn't specifically try to tease out
2 is there a different safety profile in any of those
3 age ranges across all of those age ranges.
4 Certainly, at the 10 to 15 milligram per kilogram
5 dose, it has a good safety profile, but we didn't
6 specifically look at individual age ranges within
7 the 6 to 23 months.

8 DR. GELOTTE: In terms of PK, we didn't
9 break down the group between 6 months and 23 months
10 of age. But in my presentation, I do have a
11 scatter plot of the individual AUCs starting at
12 6 months. Most of the presentations were box
13 plots, but in that particular figure of the
14 regression line, you can see the -- it's in the
15 presentation -- regression. It has the individual
16 observations of each child. So that gives you a
17 sense at least that you don't see a trending at the
18 lower end or the higher end.

19 Slide on. So what you're looking at here
20 are the individual observations of those children.
21 So in the two dotted lines, you see 6 to 23 months.
22 So you're going to see the individual observations

1 in 2 to 11.

2 So what we're seeing in this particular
3 dataset, and there's about 49 children on the left
4 and about 59 in the next age group, you're really
5 not seeing some type of trending. Like if it was
6 going to be higher AUC for the same dose, you would
7 sort of see a trend.

8 So we haven't actually analyzed. There's
9 not a lot of individuals to break apart the
10 subgroups in that group, but we're not seeing
11 differences in exposure for the same dose.

12 DR. WALCO: I guess where I'm coming from,
13 Dr. Hertz alluded before to the work that the panel
14 had done for the FDA in terms of extrapolation and
15 looking at the younger age groups. And one of our
16 major foci in that work was understanding the
17 development of the liver, for example, and how it
18 metabolizes drugs. And a critical question would
19 be at what age can we feel confident that the liver
20 is behaving in an infant similarly to how it would
21 behave in an older child or an adult. And,
22 certainly, the younger the child, the greater the

1 prospect there is for variability.

2 I would argue, looking at your scatter plot,
3 that certainly the variability that you had up
4 there at that younger end of the spectrum is
5 significantly greater than it is in adults.

6 DR. GELOTTE: Slide on. What you see here,
7 again, whenever you're going to pool data across
8 several studies, this particular group of adult
9 studies that was chosen for this analysis was
10 chosen for a few reasons.

11 These PK data were done in the 1980s, and in
12 this particular -- I chose one dose so that it
13 would match the, I guess, 10 to 15 milligram per
14 kilo dose.

15 What you saw this morning with Dr. Ji's
16 presentation, the reference compared to adults is
17 the full monograph OTC range from 325 to about
18 1,000 milligrams. This is a very narrow cut and
19 not really representative like a broad. It's the
20 healthy -- what I would call healthy control
21 population versus looking at the children in terms
22 of the study design.

1 They're not strictly fasted and we know that
2 food can affect the absorption a little bit because
3 they're more done in the clinical setting. Each of
4 those estimates of AUC that you see there are maybe
5 from limited blood samples. So we take maybe seven
6 or eight for each of those adults. We upped that
7 double dose. I can take 18 blood draws. So we
8 have a more precise measurement of AUC. So what
9 you're seeing is some measurement error. You're
10 seeing some error with respect to the study design,
11 as well.

12 But your point is well taken. I think in
13 terms of we don't have the data below 6 months of
14 age and a lot of the maturation in terms of
15 neonates and that there are differences in
16 clearance, but what we do know, and I think it was
17 presented this morning by Dr. Ji, again, was that
18 even though the glucuronidation has not yet
19 been -- is mature, sulfate, it compensates. It's a
20 very efficient method and they switch and, at the
21 end of the day, they're very efficient in terms of
22 the clearance.

1 DR. NEILL: So I still have Drs. Engle,
2 Rogers, Farber, Reidenberg, and Cohen. If I didn't
3 call your name and you have questions, stick your
4 hand up again, and we'll get your name on the list
5 here.

6 Dr. Engle?

7 DR. ENGLE: My question is for Dr. Kuffner.
8 I'm trying to better understand the label that you
9 presented. You had a two-cut and you had a five-
10 cut. So am I understanding correctly that even
11 though we'll have the same concentration, you're
12 still planning to have two different products, one
13 for kids less than 2 and one for children greater
14 than 2?

15 So that's the case. All right. Then on the
16 product that's greater than 2, what dose is going
17 to be on there? Is there going to be a dose or is
18 it going to say see your doctor for children less
19 than 2?

20 DR. KUFFNER: There are going to be two
21 different products, same concentration, and the
22 reason for that is so that you can have age-

1 appropriate dosing devices. So across the entire
2 industry, we're moving to a syringe for the younger
3 children, which is age-appropriate for them, and
4 then we'll have a dosing cup for the older
5 children.

6 What will it say on the label?

7 DR. ENGLE: Right, because what I'm thinking
8 of -- I work with a lot of economically
9 disadvantaged patients and a lot of times, mom has
10 the 4-year-old and the 1-year-old, and they can
11 only afford to buy one product. So I'm wondering,
12 are we still going to have an issue where patients
13 who can't afford to buy the two different products
14 still don't have dosing information on the label?

15 So that's where I'm going with this. I'm
16 just curious what you're thinking about that.

17 DR. KUFFNER: I don't know exactly. I think
18 that's something that we would have discussions
19 with FDA about in terms of what would be that exact
20 language to consumers. But I think having
21 appropriate language so that there isn't confusion
22 is important.

1 DR. ENGLE: Because otherwise, I think even
2 though it's the same concentration, it still could
3 be confusing to a consumer.

4 DR. NEILL: Dr. Rogers?

5 DR. ROGERS: This question is for
6 Dr. Kochanowski. You talked about Know Your Dose,
7 that you're doing this educational program, and
8 it's on the Web, you have a website.

9 I can tell you that the one thing that we do
10 know is that people -- almost everyone, no matter
11 how poor you are, has a cell phone. That much we
12 know. And not all cell phones have websites,
13 access to websites. The underserved
14 population -- as a consumer representative, the
15 underserved population probably doesn't have a
16 computer nor do they use the library frequently.
17 The Latino population, those that are underserved
18 and economically deprived, disadvantaged, may not
19 be able to read as well.

20 So I'm wondering. Is this going to be
21 bilingual, as being the fastest-growing minority
22 population in the United States, and at what level

1 will it be bilingual?

2 When it comes to -- secondly, another
3 question to Dr. Kuffner is that when you talk about
4 weight and age dosage, I'm not sure that people who
5 are illiterate are going to understand that.

6 DR. KOCHANOWSKI: Well, I will start with
7 the Know Your Dose campaign. I listed the partners
8 in the Acetaminophen Awareness Coalition. This is
9 just launching, and our goal is to develop the
10 right materials that our partners need to reach any
11 and all populations that need to be served.

12 So great idea. I had a conversation with
13 someone this morning about a phone app and couldn't
14 we do something like that. For example, the
15 National Association of Hispanic Health is one of
16 our partners that has ideas for reaching that
17 population. And I think we have the ability to
18 tailor and develop content and get it to the right
19 place and through the right people, and we welcome
20 any and al partners to this effort.

21 DR. ROGERS: I would suggest that you put
22 the Hispanic Nurses Foundation on as one of your

1 partners.

2 DR. KOCHANOWSKI: Certainly.

3 DR. ROGERS: The reason being is that nurses
4 tend to know more about the patients or the
5 clients, and/or clients.

6 DR. KOCHANOWSKI: Thank you. And I think
7 Dr. Kuffner can speak to bilingual labels.

8 DR. KUFFNER: So when it does come to
9 bilingual labels, we have had for a number of years
10 bilingual label for our infant's Tylenol products,
11 and they're certainly available and in the
12 marketplace.

13 DR. ROGERS: That's interesting, because
14 this morning, I thought that it was discussed that
15 we did not have bilingual or that they had to call
16 a 1-800 number to get it. And the problem with
17 calling the 1-800 number is that they're told to
18 call back or put on hold, and that becomes an issue
19 to the consumer.

20 DR. KUFFNER: I certainly can't speak for
21 all manufacturers, but our infant's Tylenol, we do
22 have SKUs or shelf-keeping units that do have both

1 English and Spanish labeling. For Tylenol, we have
2 our Tylenol website that you can click and the
3 entire Tylenol website will go into Spanish.

4 For those people who may not have access to
5 the Tylenol website, as you suggested, not everyone
6 has access to online information, the 1-800 number
7 of the Consumer Care Center is on the package of
8 every Tylenol product and we have 24-hour coverage
9 of people that they could get the information both
10 in English, as well as Spanish, and speak to a
11 representative who could give them information in
12 Spanish.

13 So each company is a little bit different,
14 but that's something that we've had for a number of
15 years.

16 DR. NEILL: I have about seven or eight
17 people still with questions. We're going to take a
18 break at 3:15. After that, we're going to have an
19 open public hearing, which has four speakers at 10
20 minutes each.

21 I mention this because if we don't get to
22 all of the questions that you have now, I'd like to

1 beg the indulgence of our most recent speakers, if
2 you could stay, we will have more time for
3 questions, and it's clear that there's interest.
4 So don't feel like we're going to put you off
5 indefinitely.

6 Dr. Cohen?

7 DR. COHEN: Mike Cohen. I'd like a
8 clarification on something. On several of the
9 tables and also in the briefing materials, and also
10 on a recent guidance on measurement devices, there
11 is still the use of tsp, teaspoon, et cetera.

12 I'm just wondering if we're going to
13 standardize the concentrations of acetaminophen and
14 we're using an oral syringe, why do we need to
15 continue with teaspoon or tsp? And isn't it time
16 to utilize the metric system to allay this
17 confusion that continues to happen accidentally?
18 Somebody prescribes teaspoon instead of drops or
19 milliliters, and that has been a cause occasionally
20 of these overdoses.

21 So are you intending and does FDA even
22 intend to move towards the metric system, toward

1 milliliter? If you're looking for an oral dosing
2 device for all the oral liquids, I don't understand
3 why we would need to continue seeing that on tables
4 and charts and et cetera, et cetera.

5 DR. KOCHANOWSKI: It's a very good point and
6 as part of the CDC PROTECT initiative, we had
7 vigorous discussions about that very point. And
8 you will be seeing several manufacturers have
9 chosen to go strictly to milliliter only.

10 We did, in our own guidance for industry,
11 allow teaspoon as a backup, because there was
12 considerable discussion about were people willing
13 to simply never pick up a spoon or what if they
14 lost the dosing device. And so we eliminated
15 tablespoon for pediatric products and we said
16 teaspoon only as a backup. But there will be many
17 just going to milliliter, and that just does
18 simplify it on the dosing device.

19 We discussed this with FDA, and someone may
20 want to address it from FDA, but there's a lot of
21 complexity involved in changing regulations to
22 simply go and pick one unit of measure. It doesn't

1 mean it can't be done, but it would be a very
2 complex process.

3 DR. COHEN: It seems like the timing is
4 right.

5 I had one follow-up question real quick and
6 it's regarding the flow restrictors, which I think
7 that's a great idea. But I'm wondering if they are
8 integral to the products for the little ones or if
9 they can be removed, which would be done, I'm sure,
10 in some cases, back to the teaspoonful dosing.

11 Also, it may sound silly, but what kind of
12 instructions will there be for cleaning these,
13 because, obviously, we're using them in sick kids
14 and so on and so forth?

15 DR. KUFFNER: So for the McNeil flow
16 restrictors that will be added to our infant's
17 Tylenol products, as well as our children's Tylenol
18 products, the flow restrictor is an integral part
19 of the bottle and it actually can't be removed.

20 One of the reason we went to that was, one,
21 because we didn't want parents removing it. We
22 want to make sure that people are using the

1 appropriate dosing device that comes especially
2 with the infant's products; and, also, we didn't
3 want to have potential unintended consequences of
4 even choking. So it is completely locked in. It's
5 an integral part of the bottle.

6 DR. COHEN: Thank you.

7 DR. NEILL: Dr. Reidenberg?

8 DR. REIDENBERG: A couple of questions.

9 First, Dr. Kuffner presented three pain studies
10 that certainly looked, on seeing them, as well-
11 controlled, placebo pain studies showing efficacy.
12 I'd sure appreciate an FDA review or critique of
13 those particular studies before we have to vote on
14 whether it has analgesic effect or not.

15 The second thing is that we're talking a lot
16 about age and weight and the precision of
17 pharmacokinetics that I suspect exceeds its
18 clinical relevance. For example, all of the data
19 presented probably was normal or ideal body weight,
20 but I see lots of fat kids in this age range and
21 you can almost wonder to what extent would weight
22 rather than age-assessed dosing get you the right

1 exposure in a big, fat kid compared to the normal.

2 Then in that context, is there any market
3 research to show, in actual use on the labels,
4 whether the parents really use the age or the
5 weight?

6 DR. NEILL: Dr. Hertz?

7 DR. HERTZ: Do you want me to discuss these
8 articles now in terms of time?

9 DR. NEILL: By my watch, I've got about four
10 minutes. And being a man in my 50s, we will take a
11 break at 3:15.

12 [Laughter.]

13 DR. HERTZ: So I'll respect that and I'll
14 just give you a quick response, and then if you
15 would like more discussion, we can have some more.

16 So you might have noticed us scrambling just
17 to double-check what those articles were. To me,
18 to my read, these don't fall in a place that's
19 sufficient to support a regulatory decision,
20 because they're quite confounded, I think.

21 As we've discussed, the measurement of pain
22 is quite challenging in pediatric patients, and

1 these studies used parent report, which is often
2 necessary because the 2-month or the 7-month-old is
3 not going to really tell you much directly, but
4 they were studies in which they were looking at
5 fever, local reactions and duration, that kind of
6 thing.

7 They were also judging pain based on whether
8 the kid was willing to move their arm. And what
9 you have is an effect where fever was reduced, some
10 of the local reactions were reduced, irritability,
11 fussiness was reduced.

12 So whether that's really the right
13 population then to decide you have an analgesic
14 effect on top of everything else being different
15 between acetaminophen and the placebo group in a
16 post-immunization population is a question, and our
17 interpretation would be that it would be hard to
18 really use that as the sole basis for a finding of
19 efficacy in this age range.

20 DR. KUFFNER: So I think it's important to
21 note that I don't think it's any one individual
22 study. I think it's the totality of the data. And

1 so FDA presented studies where there was a trend.
2 I agree with Dr. Hertz that it is extremely
3 difficult. In fact, I don't think in children
4 under 2 years of age you're going to be able to
5 have the children subjectively rate their pain. So
6 you're going to have to rely on some level of
7 parental judgment.

8 There have been some other studies looking
9 at physiologic endpoints. There was a study by
10 children with heel stick where they looked at the
11 percent saturation with the heel stick and showed
12 that compared to placebo, the acetaminophen group
13 children had higher percent oxygen saturation.

14 Now, whether that's better than parents who
15 know their own children assessing pain, I would
16 argue that parents knowing their own children
17 assessing pain are probably a better judge of what
18 their pain is.

19 When you take the totality of the data, the
20 PK data that suggests there's similar exposures in
21 the younger children compared to the older
22 children, and when you do have data in the older

1 children age group, like the Schachtel paper, it
2 does suggest that acetaminophen can separate from
3 placebo, and I think the totality of the data dose
4 support the analgesic indication.

5 DR. NEILL: So let's try and squeeze in one
6 more question. Dr. Farber?

7 DR. FARBER: Neil Farber. Two quick
8 questions for Dr. Kuffner, one follow-up on the
9 pain issue. And that is, were those scales
10 validated and if so, how, the pain scales?

11 The second question is you were mentioning
12 about the solid chewable acetaminophen, and I guess
13 the question is if we're concerned, as we should
14 be, about the difference in liquid doses and trying
15 to eliminate dosing errors, despite the fact that
16 there haven't yet been many errors, shouldn't we
17 try and do everything possible; i.e., have one
18 single dose, which, although it might increase
19 splitting to some degree, there is already the need
20 for splitting based on age.

21 DR. KUFFNER: So addressing the first
22 question. In the two studies in children under

1 2 years of age, the Ipp study and the Lewis study,
2 I don't believe that those parental categorical
3 scales were validated.

4 The Schachtel study used the pain
5 thermometer for children, age appropriate, as well
6 as the smiley face scale, and those were used in
7 some other pain studies in children with sore
8 throat in that age range.

9 When it comes to the one strength of solid
10 dose formulations, adverse events from that
11 haven't -- from confusion between the 80 and the
12 160, these products have been on the market for
13 years and years and years. Adverse events aren't
14 picked up in our own postmarketing database.
15 They're not picked up, as far as I'm aware of, in
16 other databases. And so this really does seem to
17 be a different issue than the liquid concentration,
18 and I really do believe it's related to the fact
19 that on the solid dose, you always have dosing
20 information for the children who are using it.

21 On the concentrated liquid formulation, you
22 did not have dosing information. And had there

1 been dosing information on the concentrated liquid
2 products, I really believe that many of those
3 medication errors may have been prevented.

4 What makes me believe that is I have read
5 all of these reports. In many of those cases,
6 including cases presented by the FDA this morning,
7 there was a health care provider who was actually
8 involved. And the confusion was in translating
9 information, which we know is difficult for
10 everyone who practices, information from the health
11 care provider to a parent.

12 If the parents actually had dosing
13 information on the label, they would at least be
14 able to compare the information that was provided
15 to them by the health care provider. And I think
16 that is a critical difference between the solid
17 strengths and the liquids.

18 DR. NEILL: Thank you very much. I still
19 have Drs. Santana, Parker, Rosenthal, Landis, and
20 Walker-Harding on for questions. So I will keep
21 that record and we'll get back to that.

22 We're going to take a 15-minute break. You

1 should plan on being back here at 3:33,
2 approximately, when we will have the open public
3 hearing. I remind the committee members not to
4 discuss the meeting topic during the break amongst
5 yourselves or with any member of the audience.

6 See you in 15 minutes.

7 (Whereupon, a recess was taken.)

8 **Open Public Hearing**

9 DR. ROSENTHAL: All right. We're going to
10 get started here in a minute or so. So if people
11 can start finding your seats, we'd appreciate it.
12 We want to get to the open public forum. So thank
13 you.

14 [Pause.]

15 DR. NEILL: Both the Food and Drug
16 Administration and the public believe in a
17 transparent process for information-gathering and
18 decision-making. To ensure such transparency at
19 the open public hearing session of the advisory
20 committee meeting, FDA believes that it is
21 important to understand the context of an
22 individual's presentation.

1 For this reason, FDA encourages you, the
2 open public hearing speaker, at the beginning of
3 your written or oral statement, to advise the
4 committee of any financial relationship that you
5 may have with any company or group that may be
6 affected by the topic of this meeting.

7 For example, the financial information may
8 include a company's or a group's payment of your
9 travel, lodging or other expenses in connection
10 with your attendance at the meeting.

11 Likewise, FDA encourages you, at the
12 beginning of your statement, to advise the
13 committee if you do not have any such financial
14 relationships. If you choose not to address this
15 issue of financial relationships at the beginning
16 of your statement, it will not preclude you from
17 speaking.

18 The FDA and this committee place great
19 importance in the open public hearing process. The
20 insights and comments provided can help the agency
21 and this committee in their consideration of the
22 issues before them.

1 That said, in many instances and for many
2 topics, there will be a variety of opinions. One of
3 our goals today is for this open public hearing to
4 be conducted in a fair and open way, where every
5 participant is listened to carefully and treated
6 with dignity, courtesy, and respect. Therefore,
7 please speak only when recognized by the chair.

8 Thank you for your cooperation.

9 So I'd like to begin with the first open
10 public hearing presenter, Kevin Nicholson.

11 MR. NICHOLSON: Thank you. Good afternoon
12 and thank you for this opportunity to speak with
13 you today. As stated, I'm Kevin Nicholson, Vice
14 President and Pharmacy Advisor for the National
15 Association of Chain Drug Stores, and I have no
16 financial requirements to disclose.

17 NACDS represents traditional drug stores,
18 supermarkets, and mass merchants with pharmacies.
19 Our 137 chain member companies include our regional
20 chains, with a minimum of four stores, to national
21 companies. Our members fill nearly 2.6 billion
22 prescriptions yearly and have annual sales of

1 \$830 billion.

2 As FDA has recognized in the past and today,
3 acetaminophen is an extremely safe medication when
4 used at recommended doses. In addition, it is one
5 of the most commonly used medications in the United
6 States. With this in mind, it is important to
7 ensure that any new policies or regulations
8 affecting the availability of acetaminophen
9 products are workable considering the great
10 consumer need for and widespread use of these
11 products. Placing unnecessary burdens to access to
12 would cause consumers to use other pain relievers
13 and fever reducers that do not have the same highly
14 reliable safety profile.

15 Acetaminophen is the most commonly used
16 medication for relieving pain and reducing fever in
17 children. It is safe and effective for pediatric
18 use when used as directed and/or labeled.

19 I would like to highlight some of the
20 recommendations that NACDS made in June 2009 with
21 regard to pediatric acetaminophen products at the
22 Joint Meeting of the Drug Safety and Risk

1 Management Advisory Committee with the Anesthetic
2 and Life Support Drugs Advisory Committee and the
3 Nonprescription Drugs Advisory Committee. I had to
4 read that one directly from my notes.

5 At that time, we supported the inclusion of
6 dosing instructions for children under 2 years of
7 age on labels of OTC single-ingredient
8 acetaminophen products intended for children.

9 Parents often seek health care providers'
10 advice on how to dose acetaminophen for children
11 under 2 years of age. It would be ideal for
12 parents and health care providers to be able to
13 follow FDA guidelines for this.

14 I would like to reiterate NACDS' support for
15 this labeling modification, as well as amending the
16 OTC internal analgesics monograph to reflect this
17 labeling.

18 At the June 2009 meeting, the FDA advisory
19 groups voted to limit pediatric liquid
20 acetaminophen formulations to one concentration.
21 We supported this recommendation, also, as this
22 should help simplify dosing instructions and reduce

1 confusion among consumers, caregivers, and health
2 care practitioners.

3 We are pleased that the makers of single-
4 ingredient pediatric acetaminophen products have
5 announced that they are converting all pediatric
6 liquid acetaminophen formulations to one
7 concentration. This, as well as other improvements
8 and initiatives they have announced, will help
9 patients and caregivers accurately dose pediatric
10 acetaminophen products and help prevent medication
11 errors. In fact, we support many of the recent
12 initiatives that the manufacturers of these
13 products have announced.

14 We would also like to voice our support for
15 weight-based dosing instructions for all children's
16 single-ingredient liquid acetaminophen medicines,
17 as weight-based dosing for children has been
18 recommended by FDA advisory committees in the past.
19 We believe that will allow for more accurate dosing
20 and help to reduce adverse incidents.

21 As we did in 2009, we encourage FDA to renew
22 efforts to educate consumers and health care

1 professionals about the dangers of liver toxicity
2 associated with overdosing on acetaminophen and to
3 encourage other safe use practices.

4 As FDA may be aware, NACDS is one of the
5 many members of the Acetaminophen Awareness
6 Coalition that was initially spearheaded by the
7 Consumer Healthcare Products Association and the
8 American Pharmacists Association to address
9 acetaminophen-related issues and educational needs.

10 Besides manufacturer and pharmacy
11 associations, the coalition members include
12 associations representing other health care
13 providers, such as pediatricians, as well as
14 associations representing consumers, along with FDA
15 and CDC as advisors.

16 The coalition works through its member
17 groups to educate consumers and patients on how to
18 use medicine containing acetaminophen appropriately
19 and to change behaviors that could lead to
20 unintentional acetaminophen overdoses.

21 Based on the research the coalition
22 conducted, the coalition is launching the Know Your

1 Dose campaign to remind consumers about the
2 importance of reading and following label
3 directions; to educate consumers about the
4 importance of knowing whether their medication
5 contains acetaminophen and not to take two
6 medicines that contain acetaminophen at the same
7 time and to reassure consumers that medicines
8 containing acetaminophen are safe and effective
9 when used as directed, but can cause serious liver
10 injury or death if overdosed.

11 In summary, we agree that pediatric
12 acetaminophen should be marketed as a single
13 concentration for liquid pediatric formulations and
14 FDA should include dosing information for children
15 under 2 years of age in the monograph.

16 Also, we recommend acetaminophen dosing be
17 provided as weight-based for all children's single-
18 ingredient liquid acetaminophen products. And
19 finally, we support increased consumer education
20 about the varying formulations and concentrations
21 of acetaminophen, presence of acetaminophen in many
22 combination products, and the implications of

1 potential overdose.

2 Thank you again for this opportunity to
3 address you today.

4 DR. NEILL: Thank you. Our next speaker is
5 Dr. Mike Royal.

6 DR. ROYAL: Good afternoon, and thank you
7 for the opportunity to speak. As you see, my name
8 is Mike Royal. I'm an internist and
9 anesthesiologist, and, also, a pain and addiction
10 medicine specialist. I'm an officer, shareholder,
11 and employee of Cadence Pharmaceuticals. You can
12 see my title there.

13 Cadence is the manufacturer of Ofirmev
14 acetaminophen injection, which doctors this morning
15 mentioned and noted that we were recently approved
16 in November of last year, and launched just
17 recently this year.

18 The rationale for our being here is that we
19 provided to FDA a sizeable amount of not only PK
20 and safety data, but some dosing simulations which
21 we believe might be of interest to the committees
22 to consider today.

1 So as an overview of my comments, we're
2 going to talk a little bit about our PK data,
3 specifically, the data under age 2 and the
4 population PK model and the dosing simulations that
5 we produced.

6 As a result of these simulations,
7 particularly under age 6 months, we believe that
8 dosing modifications are warranted, but the
9 remainder of the dosing simulations do indeed
10 support McNeil's proposed dosing recommendations
11 for children from age 6 to 23 months.

12 But we would also recommend that a daily
13 dose maximum be warranted and considered for all
14 routes of administration, since there is now the
15 potential for some concomitant dosing of a variety
16 of routes of administration.

17 First, a short regulatory history. IV
18 acetaminophen under other trade names has been
19 approved in well over 60 countries, starting with
20 France in 2001. We have obtained approval for
21 Ofirmev, as you heard, on November 2nd. And as
22 part of our pediatric clinical development program,

1 we provided data in 355 pediatric subjects across
2 all age strata, from pre-term neonates all the way
3 up to adolescents, and part of that development
4 program included 125 repeat dose PK subjects from
5 pre-term neonates up to adolescents, and that
6 database was used to create our population PK
7 model.

8 Of course, we are only approved from age 2
9 and up for the treatment of fever and the
10 management of pain. We have agreed with FDA to
11 perform a post-approval study that hopefully will
12 be instructive to the issue being discussed today,
13 which is a PK/PD analgesic correlation under age 2.

14 As you know, oral acetaminophen is very well
15 absorbed and highly bio-available. Our estimates
16 from our studies is anywhere from 85 to 94 percent
17 bio-available. IV acetaminophen, of course, avoids
18 the variability of oral absorption, and it also
19 avoids first pass hepatic exposure.

20 As part of our studies, we did new
21 analytical methods, so we were able to drive down
22 the dose -- or the amount of blood needed to

1 25 microliters, which allowed us to get a slightly
2 richer PK sampling than historically was done in
3 the '80s and '90s. As a result, we've been able to
4 compile quite a bit of PK repeat dose data in
5 children under age 2 and neonates and infants, and
6 what I'd like to do is share some of that data with
7 you. Of course, we used weight-based dosing and
8 our PK modeling would predict that some dose
9 modifications are necessary in the younger age
10 groups.

11 As you can see here on this very busy
12 figure, the individual data points that you see
13 reflected there are all of the different subjects
14 in the age strata from neonates all the way up to
15 the adults. On the far left, you'll see quite a
16 few data points, and that represents the 78
17 neonates and infants that were included in our
18 repeat dose study.

19 This is a normalized clearance line that you
20 see, the solid line, and, as you see, it's
21 relatively flat from about two years all the way up
22 to the elderly. Under age 2, however, there is a

1 decrement in clearance and that's a result of well
2 characterized maturational changes that were
3 discussed earlier this morning. As you can see,
4 based on these pop PK modeling information,
5 reduction in dose probably would be warranted under
6 age 2 and certainly under age 6 months.

7 This is now box plots of AUC. And on the
8 left, what you see is after a single dose of 15
9 milligrams per kilogram, the exposures are
10 relatively similar from infants all the way up to
11 adults. You see neonates slightly higher exposure
12 at 15 milligrams per kilogram, but you really start
13 pulling out differences when you look at steady-
14 state dosing. And on the right, what you see is
15 now 15 milligrams per kilogram q6, and now you see
16 that both infants and neonates would warrant a dose
17 regimen modification as a result of these simulated
18 data.

19 We then took our pop PK meta-analysis and
20 the model and did dosing simulations with dose
21 ranges from 7.5 to 15 milligrams per kilogram and
22 dose intervals from four to eight hours in order to

1 evaluate the types of exposures and concentration
2 value that might be predicted based on our model.

3 What you see here is that a dose of 10 to 15
4 milligrams per kilogram q6 in pediatric subjects
5 from neonates all the way up through the older
6 infants is supported by our pop PK modeling. Note,
7 of course, again, that we are not approved for
8 under age 2, but we did supply all this data to FDA
9 as part of our NDA package.

10 So if you look at a table of all of these
11 things and perhaps, very importantly, the maximum
12 daily dose that would be predicted based on this
13 modeling, the bottom row is children, and, of
14 course, what you see there is our approved label
15 dosing of 15 milligrams, actually, q4 to 6 to a
16 maximum of 75 milligrams per kilogram per day, but,
17 also, you could give a dose of 12.5 milligrams per
18 kilogram q4 hours if you chose to do that on an
19 around-the-clock regimen.

20 What you see in the younger age groups is
21 our predicted dosing regimens that would produce an
22 exposure and concentration values similar to

1 children age 2 and older. So that if you believe
2 that matching the same exposure values and
3 concentration values would produce the same level
4 of efficacy, that's what we were trying to achieve
5 here.

6 You can see that from neonates,
7 10 milligrams per kilogram q6 hours to a maximum of
8 40 milligrams per kilogram per day; in younger
9 infants up to 1 year of age, 12.5 milligrams per
10 kilogram q6 hours to a maximum of 50 milligrams per
11 kilogram per day; and, in older infants from 1 to 2
12 years of age, 15 milligrams per kilogram q6 to a
13 maximum of 60 milligrams per kilogram per day.

14 All of these doses would produce exposure
15 values that are very similar to children age 2 and
16 older.

17 So in summary, we wanted to show the
18 committees our pediatric data, particularly under
19 age 2, to the extent that that would be useful in
20 your considerations today. And thank you again for
21 the opportunity to be here. Our PK data and our
22 dosing simulations do support the McNeil oral

1 dosing recommendations for children age 6 to
2 23 months. Our simulations do, however, suggest
3 that dosing regimens for infants under age 6 months
4 ought to be modified, and an age-specific daily
5 dosing maximum ought to be considered as well as
6 your weight-based dosing for interval dosing.

7 Of course, as we plan to do and have done so
8 by agreement with FDA, we plan to do an IV PK/PD
9 analgesia correlation to establish a relationship
10 between the plasma values and the efficacy that's
11 observed in pain using validated pain scores in a
12 postoperative pain model. We'll try to do that
13 under age 2 and, hopefully, at some point in the
14 not so distant future, you'll have that data.

15 Thank you very much.

16 DR. NEILL: Thank you.

17 Our next speaker is Dr. Daniel Frattarelli.

18 DR. FRATTARELLI: Hi, everybody. My name is
19 Daniel Frattarelli. I'm the chair of the American
20 Academy of Pediatrics' Committee on Drugs. I'm
21 representing them today. And I'm just a practicing
22 pediatrician. I have no conflicts of interest,

1 financial or otherwise, with anybody.

2 I'd like to discuss today the academy's
3 position on this. And after this, I'm going to be
4 referring to this as the AAP.

5 As you guys know, this is a nonprofit
6 professional organization of 60,000 primary care
7 pediatricians, pediatric medical subspecialists,
8 and pediatric surgical specialists. And I'd like
9 to thank you for the opportunity to provide
10 comments today on the over-the-counter drug
11 products containing acetaminophen.

12 As a practicing pediatrician, I care for
13 children almost daily who benefit from
14 acetaminophen. However, I also care for children
15 whose parents are confused about the proper dosing
16 of acetaminophen-containing products, and, as a
17 result, they may unintentionally over or underdose
18 their children. In some cases, and, fortunately,
19 these are not from my personal experience, this
20 confusion has led to emergency department visits,
21 hospitalizations, and, tragically, even some
22 deaths.

1 Now, the AAP has worked for decades to
2 ensure that medicines used for children are studied
3 in children. As we all know, the physiology of
4 children is different from that of adults, and this
5 changes how they absorb, distribute, eliminate and
6 respond to medications. And it's because of these
7 significant differences that it's imperative to
8 remember that children are not just little adults
9 and that they must, whenever possible, have the
10 benefit of age-specific therapeutic safety and
11 efficacy data specific to them.

12 Now, two laws, the Best Pharmaceuticals for
13 Children Act and the Pediatric Research Equity Act,
14 have taken giant strides towards achieving this
15 goal. The academy has greatly appreciated its
16 partnership with the FDA on the implementation of
17 these two laws and is proud that, to date, nearly
18 400 drugs have been relabeled with pediatric
19 information as a result. The AAP looks forward to
20 working with FDA and others to renew and strengthen
21 these laws when they're up for reauthorization in
22 2012.

1 Now, with regard to the questions in front
2 of us, the first thing I'd like to talk about is
3 weight-based dosing. The AAP believes that dosing
4 based on weight and/or body surface area
5 constitutes a more accurate basis for determining
6 optimal dosing for an individual child than does
7 age alone. The AAP called for weight-based dosing
8 nearly 14 years ago when the FDA sought to improve
9 OTC product labeling, and we, once again, today
10 renew that call.

11 Dosing based on age ranges, such as 2 to 6
12 or 6 to 12 years, is too broad. An 11-year-old
13 child is very different from a 6-year-old. I mean,
14 you guys can see this if you go to the school play
15 and you see all your third graders lined up there,
16 right? There's going to be some that are a lot
17 larger than others, and that's all for kids that
18 are the same age.

19 Weight should replace age for dosing
20 purposes, although age could be used as a backup in
21 cases where the child's weight is not known.
22 However, most parents have a reasonable knowledge

1 of the weight of their child. Children are weighed
2 every year at their well child visits. And pretty
3 much anytime a child comes in, even if she is sick,
4 we'll go ahead and check the weight then and the
5 parents often ask about that.

6 Caregivers who understand that dosing should
7 be based on weight rather than age are much less
8 likely to give an incorrect dose. And for
9 simplicity, labeling that utilizes similar weight
10 and age ranges as ibuprofen may be desirable.

11 Appropriate dosing of medications for use in
12 children in the absence of studies poses an ongoing
13 dilemma for providers. Acetaminophen doses of 10
14 to 15 mgs per kilo per dose given every four to six
15 hours orally are generally recognized as safe and
16 effective for otherwise healthy children outside of
17 the immediate neonatal period. Further research is
18 needed to define the specific weight ranges
19 necessary to provide a more refined dosing schedule
20 for OTC acetaminophen.

21 Revised labeling using weight-based dosing
22 should also include specific language about the

1 duration of use; for example, only use it up to
2 three days, after which you need to go ahead and
3 have your child see the pediatrician for the over-
4 the-counter acetaminophen drug products.

5 Next is the issue of labeling of over-the-
6 counter drug products containing acetaminophen for
7 children under the age of 2 years. The AAP
8 applauds the efforts to revise the OTC monograph
9 for these drug products and joins with others to
10 advocate in the strongest possible terms that the
11 FDA take immediate action to update the OTC
12 monograph for these drug products when used in
13 children.

14 With respect to the OTC acetaminophen drug
15 products, pediatric labeling should be included for
16 all children ages 6 months through 12 years.
17 Dosing information for children less than 2 years
18 is especially important given the large number of
19 adverse events that are associated with this age
20 group.

21 Labeling should also indicate that any fever
22 greater than 100.4 in a child less than 3 months

1 requires an evaluation by the child's pediatrician.
2 Additionally, labeling should advise parents and
3 caregivers to seek physician advice if the infant
4 has any prior underlying chronic medical condition,
5 liver problem, kidney problem, something like that.

6 Minimizing medication error is also an
7 important part of this discussion, we feel. And
8 simply put, there should be a single standard
9 concentration for all over-the-counter pediatric
10 liquid medications.

11 In the face of ample evidence demonstrating
12 that multiple concentrations confuse parents and
13 result in inappropriate dosing leading to injury in
14 children, there is no reason not to have a single
15 concentration for over-the-counter pediatric liquid
16 medicines. Many parents are unaware that liquid
17 concentrations for infants can be more than twice
18 those for children and can mistakenly overdose
19 their children as a result. And I've seen this
20 actually fairly recently in talking with families.

21 The AAP welcomes the recent announcements by
22 manufacturers of OTC single-ingredient liquid

1 pediatric acetaminophen products that they will
2 voluntarily convert these products for children
3 into a single concentration. However, this move is
4 voluntary. It applies only to acetaminophen
5 products and it comes nearly a decade after the
6 Nonprescription Drugs Advisory Committee voted to
7 implore manufacturers and the FDA to standardize
8 the concentration of drops for children. We would
9 urge the FDA to take a more proactive role in
10 ensuring the safety and safe use of liquid
11 medications for children.

12 All liquid forms of acetaminophen should be
13 accompanied by a dosing device that is consistent
14 with the product labeling. Dosages should be in
15 metric units, such as mls, and should not use
16 teaspoon or tablespoon measures.

17 Consistency among all dosing devices that
18 meet these criteria would be idea to help avoiding
19 medication errors by caregivers. And flow limiting
20 devices and other efforts to decrease unsupervised
21 ingestion should also be encouraged.

22 Pediatric care providers must continue to

1 educate parents and patients about the safe use of
2 acetaminophen. Although acetaminophen is both safe
3 and effective when used in accordance with
4 therapeutic doses, unintended overdoses have been
5 associated with fatal and nonfatal hepatic injury.

6 Additionally, health care providers need to
7 be aware that some children appear to be at
8 increased risk of developing acetaminophen
9 toxicity, including those with certain chronic
10 diseases and other risk factors. Additional
11 research is needed to help determine factors that
12 may contribute to individual susceptibilities to
13 acetaminophen-related liver injury.

14 Lastly, a few words about combination
15 products. To maximize patient safety, all over-
16 the-country drug products, including acetaminophen,
17 should be single ingredient. Patients are often
18 unaware that drug products, including prescription
19 ones, may also contain acetaminophen. As such, the
20 AAP feels strongly that there is no reason why OTC
21 combination products containing acetaminophen
22 should be on the market for children.

1 Although the joint committee has been asked
2 to provide guidance to the FDA on single-ingredient
3 acetaminophen drug products, the AAP strongly
4 encourages you to take up and consider the safety
5 issues surrounding OTC products containing
6 acetaminophen in combination with other
7 ingredients.

8 Cough and cold products that contain
9 acetaminophen and ibuprofen should not be given to
10 children because of the possibility that parents
11 may unintentionally give their child multiple doses
12 of an antipyretic and a cough and cold medication
13 that contains the same antipyretic.

14 Additionally, the efficacy of these cough
15 and cold products for children, including those
16 that contain acetaminophen, has not been proven.
17 In 2007, the AAP stood before this joint committee
18 and acknowledged that although some cough and cold
19 medicines were studied in children prior to their
20 introduction on the market, the trials at that time
21 do not meet current standards and that subsequent
22 studies have found the products to be ineffective

1 in children.

2 That 2007 meeting was held in reaction to a
3 citizens' petition received by the FDA that
4 challenged the efficacy of these products in
5 children and raised concerns about children's
6 injuries and death caused mostly by accidental
7 overdose.

8 I was a signatory of that citizens'
9 petition. In the face of evidence of no
10 effectiveness and certain evidence of harm, the AAP
11 recommended that cough and cold medicines be
12 relabeled as follows: "This product has been shown
13 to be ineffective in the treatment of cough and
14 cold in children under 6 years of age. Serious
15 adverse reactions, including, but not limited to,
16 death have been reported with the use, misuse and
17 abuse of this product."

18 The joint committee agreed with the AAP
19 recommendations and voted to recommend to FDA that
20 these products be labeled against their use in
21 children under 6 years of age. But today, almost
22 four years later, we have no new data to justify

1 the use of these products in the pediatric
2 population, and yet the FDA has taken no new
3 regulatory action to address the issue of pediatric
4 cough and cold medicines.

5 The AAP renews its call on the FDA today to
6 take regulatory action on the monograph for
7 pediatric cough and cold products, and we are
8 pleased to join the voices calling on FDA to revise
9 the OTC monograph for drug products.

10 The AAP looks forward to working with the
11 joint committees and with the FDA to ensure the
12 safety and efficacy of medicines used in children.
13 And I'd like to thank you guys for the opportunity
14 to speak to you today and look forward to any
15 questions that any of you might have.

16 DR. NEILL: Thank you. I remember that
17 meeting well, as do I think many of the people up
18 here.

19 Our next and last speaker is Dr. Brian
20 Kaplan.

21 DR KAPLAN: Thank you very much for this
22 opportunity to speak today. I am Dr. Brian Kaplan.

1 I am the chief medical advisor and director at
2 AccuDial Pharmaceutical. AccuDial is a member of
3 the Consumer Healthcare Product Association's
4 Acetaminophen Task Force, as well as CDC's PROTECT
5 initiative.

6 I have been compensated by AccuDial for
7 being here today. I have received my board
8 certification in internal medicine from the
9 American Board of Internal Medicine, as well as
10 emergency medicine from the American Association of
11 Physician Specialists.

12 I was an emergency room physician in Palm
13 Beach County, Florida for more than 10 years, and,
14 currently, I am an internal medicine physician in
15 Boca Raton, Florida in an MD VIP practice. During
16 my many years as a physician at this point, I have
17 treated actually in excess of 15,000 children, many
18 of whom I treated for pain or fever.

19 AccuDial Pharmaceutical is very happy to be
20 here today and, certainly, we support and recommend
21 dosing of acetaminophen for all children to be
22 primarily by weight, as it is the standard of care

1 in pediatrics, and that children should be dosed by
2 age only when their weight is not known.

3 We also support that a single concentration
4 of acetaminophen at 160 milligrams per 5 mls be
5 used for children of all ages and that concentrated
6 infant's drops should not be manufactured due to
7 their contribution to the acetaminophen overdose
8 cases.

9 As well, we recommend that the pediatric
10 liquid medications that have acetaminophen include
11 a calibrated dosing spoon or a syringe that is
12 consistent and has consistent markings with the
13 product that it is packaged in.

14 AccuDial also recommends that there be a
15 prominent display of a distinctive universal icon
16 to indicate the presence of acetaminophen in a
17 product, as well as flow restrictors in OTC liquid
18 products containing acetaminophen, which would, of
19 course, reduce the possibility of the unsupervised
20 ingestion by children.

21 We also recommend that there be better
22 child-resistant packaging of acetaminophen-

1 containing products through the newly designed
2 closure systems and bottles.

3 AccuDial Pharmaceutical also supports and
4 recommends that the maximum dose of acetaminophen
5 should be increased from 480 milligrams to
6 640 milligrams and that the dosing be allowed in
7 two-pound weight intervals, along with one-half
8 milliliter dosage increments, which would, in turn,
9 allow for a more consistent approximation of the
10 15 milligram per kilogram dosing of acetaminophen,
11 which has been shown to not only be safe, but
12 perhaps the most optimal of all dosing for
13 acetaminophen.

14 We have submitted a letter as part of the
15 docket, a letter written by Dr. James Heubi, who
16 could not be here today due to a scheduling
17 conflict.

18 Dr. Heubi is Director of the General
19 Clinical Research Center at Cincinnati Children's
20 Hospital. He is the associate dean for clinical
21 research at the University of Cincinnati College of
22 Medicine, and a practicing pediatric

1 gastroenterologist since 1979.

2 Dr. Heubi has been cited by the FDA due to
3 his expertise in the area of acetaminophen-induced
4 hepatotoxicity in children. Dr. Heubi has not been
5 compensated for his opinions and recommendations
6 that are stated in his following letter dated
7 May 3rd, 2011 and submitted to the committee. He
8 is not an employee nor does he provide consulting
9 services for or on behalf of AccuDial
10 Pharmaceutical.

11 Dr. Heubi's letter of May 3rd, 2011,
12 addressed to the members of the Nonprescription
13 Drug Advisory Committee and Pediatric Advisory
14 Committee, makes the following recommendations and
15 statements: that acetaminophen is a safe and
16 effective antipyretic and analgesic for the
17 treatment of fever and mild to moderate pain in
18 children and infants when dosed within the range of
19 10 to 15 milligrams per kilogram every four hours;
20 that weight-based should be separate from dosing by
21 age; that directions should instruct the caregiver
22 to dose the child by weight; and, that,

1 importantly, the efficacy of acetaminophen as an
2 antipyretic is dose-dependent. So dosing children
3 more consistently throughout the dosing range will
4 allow for a more consistent therapeutic response.
5 He also recommends that the maximum single dose of
6 acetaminophen for children be increased from 480 to
7 640 milligrams.

8 Dr. Heubi also supports the industry's
9 conversion to a single concentration of OTC
10 acetaminophen at 160 milligrams per 5 mls for use
11 in all infants and children. And, finally, that
12 OTC acetaminophen infant's drops in concentrated
13 form should be removed from the market all
14 together.

15 Thank you again for your attention to these
16 matters, and thank you for allowing me to speak
17 today.

18 **Clarifying Questions (continued)**

19 DR. NEILL: Thank you.

20 The open public hearing portion of this
21 meeting has now concluded and we will no longer
22 take comments from the audience. The committee

1 will now turn its attention to address the task at
2 hand, the careful consideration of the data before
3 the committee, as well as the public comments.

4 I still have Drs. Santana, Parker,
5 Rosenthal, Ms. Celento, Drs. Landis, Walker-
6 Harding, and Nelson with questions from earlier. I
7 would suggest that we address those.

8 Those of you who still have questions that
9 accrue from the open public hearing comments, we'll
10 move on to those immediately after.

11 So, Dr. Santana?

12 DR. SANTANA: So maybe Dr. Kuffner can help
13 me with this question, and it relates to moving
14 toward a single solid oral dosage form. And if I
15 recall correctly, you made two arguments for
16 maintaining both the 80 and the 160.

17 The first argument, as I recall, was that
18 there really have been no safety issues identified
19 with either misuse or overuse of those two
20 different products. The second argument I heard
21 was that having the 80 and the 160 gives you
22 flexibility at the extremes of that 2 to 11-year

1 age in terms of the number of tablets that children
2 potentially would have to take.

3 But having said all that -- I think those
4 are okay arguments. But having said all of that, I
5 mean, I sat here over the break and did a
6 calculation that if you move to, for example, a
7 single dose of 120, number one, you would cover the
8 extremes fairly well. If anything, you would be
9 putting less of a burden on the younger kids and
10 just a slightly -- half a tablet or maybe one full
11 tablet and more for the older kids.

12 So I think that's very reasonable. I think
13 potentially you could -- moving to a single dosage,
14 also address the socioeconomic issues, so parents
15 don't have to buy two different products. And
16 although I'll say this with a little bit of
17 reluctance, I can't see any plausibility of
18 additional safety issues if you move to a single
19 dosage.

20 So are there other reasons that maybe we
21 should be understanding or exploring of the
22 reluctance to move to a single solid oral dose?

1 DR. KUFFNER: I think one reason we started
2 off with an 80 milligram dose, because that was one
3 of the -- the 80 milligram dose was within the
4 monograph, I think is one reason. I think anytime
5 you change concentrations, as we're doing with the
6 single-ingredient liquids, there's always a risk of
7 confusion. Certainly, there are different
8 formulations that could be put together or
9 different strengths put together that may not
10 require the older children to take as many pills
11 and may not require you to split pills. So that's
12 certainly a consideration.

13 DR. NEILL: Dr. Parker?

14 DR. PARKER: A couple questions. One is, as
15 we discussed earlier, a change in the -- if we were
16 able to move to a standardized dosing chart that
17 had weight and age instructions on it that worked
18 across products, this would also apply to
19 combination products that contain acetaminophen.

20 So I'm just wondering, in thinking about
21 that, if you anticipate any problems with the
22 combination products following suit with what would

1 be happening in the single-ingredient products.

2 I'm more able to visualize this with a
3 single ingredient. I know we have the AAP that,
4 again, is asking for consideration to go to single
5 ingredient, and I was here and part of those
6 discussions before and realize they have been
7 ongoing discussions and advocacy to really move
8 toward that, but that's not where we are right now.
9 But I'm just wondering, in critically thinking
10 about it, how you all view whether or not this will
11 impact the combination products.

12 DR. KUFFNER: I think for children 2 to 11,
13 which is the current five-cut dosing chart that's
14 been on the market for the single-ingredient
15 products for 30 years, I think that's appropriate.
16 I think the two-cut under 2 is appropriate. So if
17 you're talking about the cough and cold medicines
18 which are used today from age 4 and above, McNeil,
19 many years ago, actually requested to actually put
20 more finely divided age cuts on the combination
21 products.

22 Currently, under the monograph, and FDA is

1 the most appropriate people to speak about that,
2 where you just have two doses, so two cuts, 2 to 6,
3 2 to less than 6 and then 6 to less than 12 for the
4 combination products, McNeil would certainly be in
5 favor of a more finely divided dosing chart, age
6 and weight with the similar cuts that are on the
7 single-ingredient acetaminophen medicines today.

8 DR. PARKER: And then the other question
9 related to the Know Your Dose efforts that are
10 underway. And I appreciate the efforts to
11 encourage people to know and understand dose and,
12 also, to keep products as safely out of reach as
13 possible with the Up and Away campaign.

14 It also seems to me that an essential need
15 to know to do is to understand what the product is,
16 and I'm wondering about a specific focus on helping
17 the public understand the active ingredient of
18 every product that they face and efforts to perhaps
19 make that not only displayed on the front panels,
20 but larger than other content on front panels,
21 which is currently larger than what the active
22 ingredient is, and how we actually anticipate the

1 public knowing what it is they are taking when it's
2 hard to locate sometimes and not prominently
3 displayed or so small, especially related in light
4 of how products are advertised to the public and
5 the regulatory oversight by the FTC rather than the
6 FDA for over-the-counter products and a requirement
7 to tell in advertising what the active ingredient
8 is for prescription products, but not for over-the-
9 counter.

10 Why is specifically knowing the active
11 ingredient not a prominent part of those campaigns?

12 DR. KOCHANOWSKI: Well, certainly, for, as
13 you say, acetaminophen and the Know Your Dose
14 campaign, that is a very prominent -- that is the
15 reason behind that campaign, for people to
16 understand where acetaminophen is found.

17 We will learn from that, because we know
18 that most consumers identify symptoms and match
19 products by symptoms, not necessarily the active
20 ingredient. So there's a lot of education to do
21 there if we were really to try to teach every
22 active ingredient.

1 Then you're familiar with the icon research.
2 Again, if that proves very successful, that
3 acetaminophen icon could, again, help us really
4 kind of move beyond the need to remember the word
5 "acetaminophen," but know that products contain the
6 same ingredient. So that's the current state of
7 our work.

8 DR. NEILL: Dr. Rosenthal?

9 DR. ROSENTHAL: Thank you. I have two
10 questions and I'm hoping that I'm not beating any
11 dead horses. But, first, I'm very aware of the
12 latency in some of these changes and was listening
13 to the language that was used in the recent
14 presentations regarding when some of these changes
15 to promote better safety for acetaminophen were
16 going to be online.

17 I've heard a few things. First, we've
18 talked about some safety interventions, single
19 concentration, flow restrictors, consistency of
20 dispensing devices.

21 When do you anticipate that those are going
22 to be implemented? And what I've heard is that

1 we're moving towards it, and what I've heard, it's
2 coming soon. But I'm wondering if you can just
3 tell me when.

4 DR. KOCHANOWSKI: Sure. The labeling
5 changes associated with the voluntary guidelines
6 that apply to all liquid pediatric medicines that
7 were approved in 2009, many of those have moved
8 into the marketplace now and industry had a goal to
9 convert all of our products to the new guidelines
10 by fall of 2011. So we intend to place a survey
11 with the CDC and the PROTECT partners later this
12 year to see just how good of a job we've done. So
13 many of those products are in the market now and
14 more will be coming.

15 Products tend to ship in the summer for the
16 cough/cold season and other seasons. So there's a
17 seasonal aspect there. So that has been underway
18 for two years and is coming online -- has been.

19 The change to single concentration was
20 agreed last year, as well as the flow restrictor
21 change. So the manufacturing, validation, all of
22 that work has been done since last year. The first

1 manufacturers that are ready to ship are shipping
2 in June. And so those products will be appearing
3 on the shelves in July, and other will then be
4 coming behind that up through January of 2012.

5 DR. ROSENTHAL: Okay. Thank you. That's a
6 specific answer to a direct a question.

7 Second, I think I like this, the icon idea,
8 but as I've been thinking more and more about the
9 icon idea, I thought, well, why don't we just take
10 Tylenol out of the cocktail.

11 I know that this is an issue that's been
12 raised by others, but it's great to have a little
13 warning on there saying, "Hey, there's Tylenol in
14 this," but if we know that it's an issue and we're
15 willing to put some kind of a warning device on the
16 box, then what's the advantage that offsets the
17 risk and why not just get rid of it?

18 DR. KUFFNER: I think the advantage of the
19 icon is multi-fold. So the icon will prevent
20 people from using multiple single-ingredient
21 acetaminophen-containing medicines at the same
22 time, and we know that's a risk factor or root

1 cause of medication errors and overdose. So it'll
2 work for single-ingredient medications. It will
3 also work for combination-ingredient medicines, not
4 just over-the-counter combinations, but
5 prescription acetaminophen-containing medicines.

6 So we have been working as we develop this
7 icon and validate it and really test it to make
8 sure that it really does communicate acetaminophen
9 to people, and the goal is actually to have it in
10 all over-the-counter medicines, as well as all
11 prescription medicines. And whether you have
12 combination products or single-ingredient products,
13 I believe the benefit of the icon will hold for
14 both of those.

15 DR. ROSENTHAL: Do you think, along the
16 lines of this icon idea, that if the icon strategy
17 is a good one, should we also have an icon that
18 just says the number of active agents in some of
19 these combo drugs? So a mom can take a box off the
20 shelf and see "8" and know that that somehow has
21 different meaning than one that has "1."

22 DR. KUFFNER: So the way that we've

1 approached the icon -- and I don't know the answer
2 to that question. But the way we've approached the
3 icon is through research. And so many people -- we
4 could come up with our own icon and different
5 people would think an icon is better, but we
6 actually went out and tested this icon with
7 consumers and caregivers of different literacy
8 levels. And so we're really trying to take a very
9 research-based approach to this.

10 I think there are additional ways that the
11 icon potentially could be impactful, different ways
12 to develop other icons to communicate other
13 information. I think the industry is open to that.
14 I think what we want to do is get the acetaminophen
15 icon validated, have conversations with FDA,
16 produce research that will support including that
17 as part of drug facts, and then measure the impact
18 of that and if that's impactful and we've
19 demonstrated that it's impactful, then potentially
20 there would be other opportunities to develop other
21 icons.

22 DR. ROSENTHAL: Thank you.

1 DR. NEILL: Ms. Celento?

2 MS. CELENTO: Amy Celento. So I understand
3 that the icon was developed out of research and
4 that's fantastic. I think it will get people's
5 attention. But as any good marketer knows, you
6 really need to be clear about what you're saying
7 and saying pain reliever/fever reducer doesn't
8 really mean anything to a parent in terms of
9 understanding that this could be toxic to my child
10 if they take far too much of it or I give them far
11 too much.

12 So I think you have a lot of work to do in
13 this area. Again, I like the idea of the icon and
14 especially when you're looking at single ingredient
15 and then combo products. You want people to be
16 aware that they should be paying attention. But
17 saying pain reliever/fever reducer, this is the
18 active ingredient, that doesn't mean it could be
19 bad for my kid.

20 So I think that you -- as I said, you have
21 work to do there. Building on what Dr. Royal said
22 in the public comment section, there really is an

1 opportunity to have a daily dose maximum, and you
2 could incorporate something like that in this icon,
3 where it's very clear to people, if my child weighs
4 40 pounds, there's a daily limit of acetaminophen
5 in whatever medications they're taking.

6 So I have a couple more thoughts, but I can
7 pause if you would like to respond to that.

8 DR. KOCHANOWSKI: In terms of warnings, one
9 of the recent changes made and implemented -- made
10 by FDA and implemented by industry has been to have
11 a very specific liver warning on all acetaminophen-
12 containing products.

13 So there's a warning, it's called liver
14 warning. It talks about severe liver damage may
15 occur. And we've carried that over into the Know
16 Your Dose campaign because those messages then are
17 equally specific, warning about the dangerous side
18 effects if taking more than the dose, so can lead
19 to liver damage. We're trying to be very clear and
20 not couching anything about the potential for
21 damage by taking more than the recommended dose.

22 MS. CELENTO: So can I ask, then, is this

1 example that we have here, is this the statement
2 that you plan to make about acetaminophen or would
3 you be combining that it can be toxic to the liver,
4 or is that just in the Know Your Dose campaign?

5 DR. KUFFNER: The example that we showed
6 there is essentially taking the current labeling as
7 it is within drug facts. And so FDA determines
8 that that fever reducer/pain reliever language is
9 in drug facts. All we are asking is that the icon
10 be included as part of drug facts.

11 So the language that you see there is FDA
12 drug facts labeling and we're not advocating
13 changing that. We're just advocating adding an
14 icon to drug facts.

15 DR. NEILL: Dr. Landis?

16 I'm sorry. Did you have a follow-up?

17 MS. CELENTO: I had a couple more things,
18 right, and we can discuss this tomorrow then with
19 FDA in terms of the language.

20 I do want to address -- we talked about the
21 potential of children being heavy, but we haven't
22 talked about premies or low birth weight. And if

1 we are potentially going down to 6 months of age
2 dosing -- and I know that there's weight, but right
3 now it's just under 23 or 24 pounds.

4 I have concerns if the infants are very
5 small, and I don't know the impact in terms of
6 liver development, but I have concerns about that,
7 that it needs to be addressed and people need to
8 have some sort of clarity around my child is a
9 preemie or is low birth weight, what should I be
10 doing here. So I just want to put that on the
11 table.

12 Additionally, I think the syringe is a great
13 tool, it's a great dosing tool, but you need to
14 package more than one in a box, because I can give
15 you 10 examples of how it will be lost, broken,
16 separated, chewed on, completely nonfunctional by
17 the time a kid uses it twice.

18 To the point about cleaning, it really needs
19 to be easily cleaned. You do not want to be giving
20 somebody a dirty dosage every time. So you'd need
21 to package more than one and that could all be very
22 costly.

1 DR. NEILL: Thank you.

2 Dr. Landis?

3 DR. LANDIS: Thank you. My question, the
4 first one, is around the public perception and
5 patient safety, and this question goes to either
6 one of you.

7 This morning, Dr. Pham had talked about
8 over-the-counter sales and various channels of
9 distribution of the products.

10 Can you comment a little bit as far as where
11 consumers can purchase these products, say, tied
12 to -- we heard mass merchandisers, pharmacies
13 versus gas stations, airports and other places
14 where there may not be a health care provider on
15 board, and some idea of what percentage of sales
16 are in those places where there's not a health care
17 provider? And then, also, the perception maybe
18 from the public, if you can buy them in very casual
19 places, is that the perception that this is a safe
20 type of product to use?

21 DR. KOCHANOWSKI: I don't have specific
22 sales data by channel for the different products

1 that you mention. The convenience store type
2 purchases, though, are more typically the adult
3 products, whether they're in airport stores or the
4 gas stations or convenience stores. Food, drug,
5 mass, where you typically also have pharmacies, or
6 at least a lot of outlets have pharmacies, is where
7 you tend to find the full line of children's
8 products.

9 DR. LANDIS: With the safety issues, with
10 the pediatric products, is there any sense that you
11 would move to facilities where there would be a
12 health care provider that could be there to ask
13 questions and intervene if there were any problems?

14 DR. KOCHANOWSKI: I think Dr. Bond had a
15 follow-up to my response, and then we can come back
16 to that.

17 DR. LANDIS: Okay. I'm sorry.

18 DR. BOND: It addresses the bigger issue
19 that you're talking about.

20 Can you have the slide -- I think it might
21 be from our 17 or something. The question you're
22 asking is what do people do and what will they do

1 if they don't know. I mean, that's how I'm hearing
2 it.

3 In the same way that the people in Texas
4 were approached to do some behavioral modeling or
5 see what people are doing -- no, from the backup
6 slides. I think R-17 or something in that. I'll
7 bring it up in a second.

8 So I guess you guys were approached to do
9 some behavioral study, what do consumers do. They
10 talked to the people, and then they approached me
11 and colleagues at Rocky Mountain. So we did a
12 study that I'm going to show you now that is
13 ongoing.

14 Slide on. So what we did is we, together
15 with the people in Denver, planned to interview 300
16 caregivers, and we said we wanted people
17 specifically who are parents of children under
18 2 years of age who came into either the clinic in
19 Denver, the urgent care in Denver, Denver
20 Children's Hospital, or Cincinnati Children's
21 Hospital, who had given a dose of acetaminophen to
22 their child within 24 hours of the time they

1 arrived. Basically, since there is no dose on the
2 label, we want to know where did you get your dose,
3 knowing that the label says call your physician, to
4 find out what was going on.

5 So we were in the process of accumulating
6 300 surveys, 96 were performed as of yesterday
7 morning, which is why you see this in this format.
8 All the children were under 2. The mean age of the
9 child was 12 months. So that means that half the
10 children were under and many of them were smaller
11 and younger, down to five days.

12 The mean caregiver respondent age was 26
13 years. The household income of 58 percent of the
14 respondents was less than 35,000. Twenty-seven
15 percent were Hispanic, almost all in Denver, and
16 21 percent were African-American. Fifty-six
17 percent were high school graduates or less.

18 Next slide. So we asked them, in an open-
19 ended way, how was the dose determined. And
20 55 percent had consulted -- they said they
21 consulted their health care professional, but only
22 11 percent had consulted their health care

1 professional in the prior 24 hours.

2 So that goes to your question about if
3 you're at the convenience store or whatever, that
4 doesn't seem to be the behavior anyway. And only
5 one-third of them had consulted their health care
6 professional in the month prior to choosing a dose.

7 What's, I think, a little more frightening
8 and goes to the whole impetus for putting doses on
9 the label is that 24 percent said they consulted
10 the label, but there is no labeling for under
11 2 years of age, and all these children were under 2
12 years of age. And then 19 percent said they
13 guessed or estimated. And from the comments they
14 made about how they did that, the answer basically
15 was "I looked at the label for 2 years, I made a
16 guess about my child in relation to a 2-year-old
17 and made a dose."

18 So I think that your question about
19 convenience stores, obviously, I want dosing on the
20 label for children because I think the parents are
21 going to use it. And I can tell you that
22 85 percent of these people had a health care

1 professional that they didn't call, and 91 percent
2 of them, when asked "Would you like dosing on the
3 label?" said yes.

4 So I think that the public is asking for
5 doses on the label to give them the information so
6 they don't have the risk that you're talking about.

7 DR. LANDIS: Again, I'm going back to
8 thought process of the public that it's a casual
9 medication because of the location that you're
10 buying it from. And I think that that speaks very,
11 very loud.

12 So, again, I don't know if you've done any
13 research on that as far as if I can buy it in a gas
14 station or I can buy it in an airport, it must be
15 safe versus going and purchasing it, say, in a
16 pharmacy or getting it from their physician.

17 DR. KUFFNER: I don't know any specific
18 research that was done in that area. But as
19 Dr. Kochanowski says, McNeil and CHPA are working
20 to communicate, obviously, the seriousness, these
21 are real medicines, the importance of all reading
22 the label, following the dose, and at the end of

1 the day, always contacting a health care provider
2 if people have questions.

3 DR. LANDIS: And then a follow-up question
4 for you. Earlier today there was a question about
5 the Spanish labeling instructions, and my apologies
6 to you, because we don't have Tylenol infant drops
7 in our store nor have we had it for the last two or
8 three months or any of the Tylenol products to even
9 check to see.

10 Could you provide us with the labeling that
11 you have in Spanish, because all the products they
12 had out front were not in Spanish. I did have my
13 students do follow-up phone numbers and they did
14 have a lot of success. We didn't have your phone
15 number just because we don't have that product
16 available.

17 But could you share that with our group so
18 we can see how you are labeling the packages for
19 Spanish?

20 DR. KUFFNER: Sure. I don't have a slide of
21 that, but that's certainly something we can get you
22 and share with the committee either by the end of

1 today or by tomorrow morning. Likely by tomorrow
2 morning. We'll be happy to share that with you.

3 DR. LANDIS: Okay. And just one more
4 follow-on question from Dr. Cohen this morning. He
5 had asked about the dosing devices that you're
6 doing with this single strength, whether it's the
7 syringe or the cup, and asking about what types of
8 cleaning instructions you would have for the
9 patient, because that a lot of the time is very,
10 very important so that they are getting an accurate
11 dose.

12 I didn't hear the answer this morning.
13 Could you cover that, please?

14 DR. KUFFNER: The syringe on the cleaning?
15 Cleaning instructions, I'm not sure if there are
16 going to be specific cleaning instructions on the
17 label. But at least for the syringe that's going
18 to come with the Tylenol products, you are able to
19 remove the stopper and they could either wash it by
20 hand or essentially, if they wanted, put it in a
21 dishwasher.

22 I don't believe currently today we have

1 cleaning instructions on there. If that's
2 something that people think is important, certainly
3 that's something we could consider.

4 DR. NEILL: So I still have six committee
5 members that are in line here to ask some questions
6 and if you haven't figured out, the energy in the
7 room is flagging a lot. So I'm shortly going to
8 call on Drs. Walker-Harding, Nelson, Goldstein,
9 Cohen, Notterman, and Reidenberg.

10 It's true that the conversation that we're
11 having so far, these clarifying questions, seem to
12 be jumping from one area to another. All of those,
13 to me, strike me as very important.

14 I think that tomorrow morning when we begin
15 focusing on the specific questions, there will be
16 much more opportunity for some give-and-take, back-
17 and-forth. I'm confident that many of you might
18 want to jump in, in the midst of a conversation,
19 and my perception, given the way the agenda is set
20 up, is that we will have ample opportunity for that
21 tomorrow.

22 For those of you -- Dr. Baker -- who have

1 remained silent today because you have words of
2 wisdom that you will impart tomorrow during the
3 conversation, thank you for doing that.

4 [Laughter.]

5 DR. BAKER: I don't know whether I should
6 take a bow or be offended. I'm going to have to
7 think about it.

8 DR. NEILL: Dr. Rosenthal insists that you
9 say your name first, but never mind.

10 Dr. Walker-Harding?

11 DR. WALKER-HARDING: I had a question for
12 probably Dr. Kuffner. With the instructions and
13 thinking about health literacy, there's been a
14 number of recent studies that show that people do
15 better with pictures, because even educated people
16 are very minimally health literate.

17 So regardless of language or education,
18 people are not health literate. And there are
19 people that have done studies showing that
20 pictorial instructions are much more effective.

21 Are you considering moving to that rather
22 than having these instructions? You would have

1 to -- I don't know how many languages I see in a
2 day beyond Spanish and English. It seems like
3 pictures, universal language, would be much more
4 appropriate.

5 DR. KUFFNER: So I am aware of some studies
6 that do show that pictograms can be beneficial. I
7 think the icon is also representative of a picture.
8 In order to include either the icon or a pictogram
9 as part of the drug facts labeling, that's
10 something that we would need to get FDA approval
11 for to include it.

12 So that's something, just like the icon, if
13 data demonstrates that it's beneficial, we're
14 certainly open to having conversations with FDA on
15 how you could include, whether it's pictograms or
16 icons, as part of the drug facts labeling.

17 DR. NEILL: Dr. Nelson?

18 DR. NELSON: Yes, thank you. I had two
19 questions I'll condense to one now. And, actually,
20 this is for Dr. Bond, because he sort of alluded to
21 it a little bit.

22 But could you just give us your opinion on

1 the safety risk or general, conceptualize, of what
2 risk there is out there? I was going to ask him
3 about what do parents do, but he's already answered
4 that. So thank you.

5 DR. BOND: I'll try to give you a big
6 picture based on what Dr. Waldron has shared this
7 morning and a little bit by Dr. Goulding.

8 If you look at the universe of dosing and do
9 the math with the paper that Dr. Waldron shared,
10 Vernacchio, where it said that 23 percent of
11 children under 2 years of age have been exposed to
12 acetaminophen in the week prior to the time of the
13 survey, the same survey said it's 10 percent for
14 children between 2 and 10.

15 If you do the math and multiply that by
16 52 weeks a year and 4 million children in every age
17 group, there's 24 million 5 and below, you come up
18 with 180 million dosage courses per year.

19 So we're talking about just in the kids
20 under 5. So if you can show me that one slide, I
21 think it's R-9.

22 I have spent most of my career playing with

1 the data that Dr. Goulding seems to have been
2 forced to play with all of a sudden. And
3 Dr. Parker knows that I've been working with a
4 database of all the emergency department visits in
5 the NDPS for an eight-year period in every hospital
6 in the United States related to -- I mean, every
7 poison center, covering every hospital. And we've
8 looked at all the medications pertinent to the
9 conversations earlier this morning and submitted
10 the publication. And the acetaminophen subset is
11 sort of a minor part, so it's not going to conflict
12 with the journal itself, where we've submitted it.

13 This is the picture for eight years. So if
14 there's 180 million dosage courses of acetaminophen
15 per year, over eight years, that's 1.44 billion
16 dose courses of acetaminophen. And if you look at
17 the one that's on the left, which is therapeutic
18 errors, that in an eight-year period in the United
19 States, out of 1.5 billion dose courses, there are
20 1620 emergency department visits related to single
21 product acetaminophen therapeutic errors, of which
22 340 were hospitalized, 155 received acetylcysteine,

1 per Dr. Curry's comment that not everybody who is
2 hospitalized is treated, and 58 of them went on to
3 have, by this marker, an AST greater than a
4 thousand, six of which died, and these include the
5 ones I talked about before from the earlier period.

6 So just to contextualize the risk, I think
7 that's the risk flow. So you heard discussion
8 earlier about whether NDPS is complete. I can tell
9 you that we've done studies with the CDC using
10 NEISS-CADES and those databases are almost
11 identical for ED visits for pharmaceuticals for
12 kids. They're within about 5,000 per year.

13 We've checked that from this -- it's
14 published from 2001 to 2003. And we've
15 looked -- I've talked to Dan Budnitz at the CDC for
16 2004 and '05, and we're quite parallel in the
17 distribution of pharmaceutical agents that are seen
18 by the estimates, by N-CADES, and the cases from
19 NPDS are quite similar.

20 So I'm fully agreeing that they may both be
21 underestimates. I know that I don't call about
22 every case I see in the emergency department.

1 Nonetheless, even if they're twice as low, if you
2 go from the universe of 1.5 billion dose courses
3 and you end up with 1,600 ED visits and 58
4 significant injuries or death, I think the safety
5 issue is -- and that's with it being used as it's
6 used now, including no labeling.

7 My hope is that we can do better for the
8 parents of the 340 or the 1620 so that those aren't
9 even issues for them, the things that we're talking
10 about today, including dosing. And as you heard me
11 before, I'm really excited that single
12 concentration is going to come off, as well. So in
13 terms of risk, that's the point I'd like to make.
14 Thanks.

15 DR. NEILL: Dr. Goldstein?

16 DR. GOLDSTEIN: Dr. Rosenthal asked me
17 yesterday why I was so quiet. Apparently, I was
18 saving it up for now.

19 I'd like to congratulate the industry
20 colleagues on moving to single dosing, but I would
21 also like to chastise them. I think
22 Dr. Frattarelli pointed out that this problem -- I

1 know personally this problem has been around of
2 different concentrations of the liquid form for a
3 long time.

4 So the fact that it's taken 10 years I
5 personally think is shameful. And I don't know the
6 specific number of children who have been injured
7 and/or died because of medication errors due to
8 this specific problem, but the fact that it's taken
9 over 10 years to get where we seem to be going this
10 summer and later this year I think is shameful.

11 So I would like to challenge the group to
12 avoid this long duration of beating around other
13 problems going forward into the future,
14 specifically around the issue that Dr. Rosenthal
15 and Dr. Frattarelli were talking about, which is
16 the combination products and the clear potential
17 for additional acetaminophen toxicity when
18 acetaminophen is given both via the combination
19 product and as a sole ingredient.

20 With the chair and the committee's
21 permission, if I could impose on Dr. Frattarelli to
22 comment on his views on the combination products

1 and acetaminophen, and the academy's and the
2 Committee on Drugs' views on that, and the
3 rationale for why these are not a good idea, I
4 think it might be helpful.

5 Dr. Rosenthal asked a question, well, why
6 not just take acetaminophen out, but we actually
7 didn't hear the specific scientific and medical
8 rationale for that. And I was wondering if we
9 could ask Dr. Frattarelli to comment on that.

10 DR. NEILL: Are you willing? I think we
11 heard very clearly AAP is in favor of doing away
12 with combination products in the OTC market.

13 DR. GOLDSTEIN: Correct, but I would like
14 him to address why.

15 DR. FRATTARELLI: I think probably the
16 biggest issue is that a lot of these are -- well,
17 let me go back. There are two issues on this.

18 First of all, there's a potential for
19 overdose on these drugs. If parents -- icon or
20 not, in the situation we currently have right now,
21 some parents don't realize that they're giving
22 their child two drugs or two preparations that both

1 contain the same drug, and that has the potential
2 for overdose right there.

3 So right off the top, I think you've got a
4 situation that has a possibility of risk. So
5 you've got possibility of risk and then especially
6 with regard to the cough and cold medicine, you
7 have absolutely no benefit in kids under 6 years of
8 age. This is like my favorite Donald Rumsfeldism.
9 Okay?

10 We don't have absence of evidence. We have
11 evidence of absence. And these drugs have been
12 studied in younger kids, and they don't work. So
13 if you have this combination of medications that
14 don't work in children combined with the potential
15 for risk, then what's the point of keeping them on
16 the market?

17 Does that kind of get at what you were
18 asking?

19 DR. GOLDSTEIN: That's exactly what I was
20 thinking. Thank you.

21 DR. NEILL: Dr. Cohen?

22 DR. COHEN: There seems to be overwhelming

1 support for the single concentration, but I think
2 we'd be remiss if we didn't address the letter that
3 we got in our packet this morning, actually, three
4 letters, because they are from the pediatric
5 pharmacy community. And these are pharmacists at
6 children's hospitals and they don't agree going
7 with the one concentration if it means eliminating
8 the 80 milligram per 0.8 ml. And I just thought I
9 should bring that up so that we can address that.

10 DR. NEILL: I actually had a question for
11 FDA staff about that.

12 Is the question that we will be tasked with
13 answering tomorrow specific to products that are
14 marketed in the OTC setting as opposed to different
15 concentrations, products, SKUs that may be
16 available in acute care settings, only through
17 wholesale, not sold at retail?

18 To what extent does the monograph process
19 prescribe that if the concentration exists, but
20 just doesn't happen to be on the shelf?

21 DR. FURNESS: No. The monograph cannot
22 limit where these products are being distributed.

1 DR. NEILL: So I noticed that these three
2 letters that you mentioned, Dr. Cohen, came
3 primarily from inpatient acute care pharmacists
4 concerned about the high volumes necessary to
5 deliver an adequate dose in very small infants.

6 So if I'm hearing FDA correctly, absent a
7 change to the monograph that prescribed that dose
8 in the market, period, industry could continue to
9 market that exclusively to non-retail settings.

10 DR. KWEDER: They could do so under an NDA.

11 DR. NEILL: Okay.

12 DR. KWEDER: They co do so under an NDA, and
13 there is nothing that prevents a company who wishes
14 to manufacture a different concentration,
15 particularly for inpatient use, from submitting an
16 NDA for something that would be outside of the
17 monograph.

18 DR. NEILL: Just like has been done for the
19 IP formulation.

20 DR. KWEDER: That's right. Yes.

21 DR. NEILL: And so if the monograph process
22 that we're going to discuss tomorrow results in

1 committee advising, and if FDA considers the advice
2 and restricts the concentration to a single, that
3 would be the one remaining avenue for delivery of
4 that concentration in the acute setting.

5 DR. KWEDER: That's right.

6 DR. COHEN: But my question really was, I
7 guess for the folks from McNeil, and that is, have
8 they communicated with this group and are they
9 convinced or satisfied that this is something
10 that's doable for those hospitals.

11 DR. NEILL: I think they heard your cue.

12 DR. KOCHANOWSKI: I think we can both
13 respond to that. As we got into this conversion
14 question, we met with representatives from ASHP, so
15 the hospital system pharmacists, and they did some
16 sensing for us of their members. Obviously, they
17 didn't talk to every individual hospital pharmacy;
18 also shared the differences in volumes that might
19 be needed to be administered.

20 They came back to tell us they were
21 supportive of the conversion to single
22 concentration, but that they did have a diverse

1 range of opinions from their members, people that
2 favored the more concentrated drops, the less
3 concentrated, solutions, and, in fact, were
4 compounding their own concentrations, for example,
5 100 milligrams per ml, because that made the math
6 easy.

7 So I think we had a range of feedback from
8 ASHP, but that did not influence what we're doing
9 with the consumer market.

10 DR. COHEN: And the only reason I ask again
11 is this is a focus group of pediatric pharmacists,
12 and I support the one concentration. I've asked
13 for that in the past, as a matter of fact. But I
14 just want to be sure that there is interaction with
15 those folks.

16 DR. KUFFNER: We did have the interactions
17 and the volumes that would be needed. So on the
18 OTC label or even going below that with the 160
19 milligrams in 5 mls are in line with other oral
20 medicines that are given to young children. So if
21 you look at different antibiotics, whether it's
22 amoxicillin or azithromycin, those volumes are in

1 line.

2 We have had conversations because some in
3 hospitals have already changed to the 160 in 5 to
4 try to minimize medication errors within their own
5 institutions. And what we heard is, from some of
6 those hospitals that already had changed, there is
7 not an issue when you go to the 160 in 5 even
8 administering it in pediatric intensive care units
9 or neonatal intensive care units.

10 DR. NEILL: Dr. Notterman?

11 DR. NOTTERMAN: I wonder, Dr. Kuffner, while
12 you were looking at some of the consumer issues
13 related to single dose, to the dosing label, if you
14 were able to ascertain either in the literature or
15 through conversations what proportion of parents,
16 particularly of older children, know the weight of
17 their children with a reasonable degree of
18 accuracy, and particularly with respect to
19 different levels of parental education. Thank you.

20 DR. KUFFNER: In terms of different levels
21 of parental education, I'm not sure of the answer
22 to that. There are a number of studies in the

1 published literature that looked at a relatively
2 wide range of ages and those studies -- in terms of
3 two parents have the ability to correctly estimate
4 their children's weight. And those studies are
5 remarkably consistent in that around 80 percent of
6 parents can estimate their child's weight within
7 10 percent. And so we don't know the educational
8 level of those people, but the data is very
9 consistent.

10 DR. NOTTERMAN: Thank you.

11 DR. NEILL: Dr. Reidenberg and then
12 Dr. Baker.

13 DR. REIDENBERG: My question has been
14 answered.

15 DR. NEILL: Dr. Baker?

16 DR. BAKER: This is Susan Baker. I remain a
17 little bit confused about the products. If we
18 have, as you're voluntarily going to, a single
19 concentration of acetaminophen for children, for
20 young children, how many products are still going
21 to be on the market with varying concentrations of
22 acetaminophen as a single drug that would be used

1 by children? It seems to me there's still going to
2 be a whole bunch of them.

3 Am I correct or am I incorrect?

4 DR. KUFFNER: There would only be one, once
5 we go to a single concentration, only one
6 concentration of the liquid. That would be 160
7 milligrams in 5. That would be it cross the board.

8 DR. BAKER: Well, but that's the liquid.
9 And then you have two different concentrations of
10 chewable?

11 DR. KUFFNER: The chewables will be the
12 80 milligram and the 160 milligram.

13 DR. BAKER: So we have three products and
14 then we have the pills, right?

15 DR. KUFFNER: There's the adult
16 325 milligram formulation, and that does have
17 pediatric labeling from 6 to 12.

18 DR. BAKER: Exactly. So we have at least
19 four pediatric products, four products that would
20 be used in the pediatric age groups still.

21 DR. KUFFNER: That's correct.

22 DR. BAKER: Thank you. One other question,

1 if I may. I'm so sorry.

2 DR. NEILL: Please.

3 DR. BAKER: I'm also confused about one
4 other thing, and that is that all of the labeling
5 continues to have spoon, half a spoon, half of this
6 spoon, something else. I know Dr. Frattarelli
7 spoke to that issue, and this is an issue that
8 pediatricians have a very difficult time with.

9 No two spoons are the same size. And I see
10 2,000 patients a year, and I can tell you that the
11 way people take the medication I prescribe is gosh
12 darn frightening. But a lot of them do use spoons,
13 and they don't use measuring spoons, they use
14 whatever spoon their mother gives them or their
15 grandmother gives them or they find around the
16 house. And a lot of women don't have any idea what
17 a teaspoon or a tablespoon is.

18 So I'm wondering, are you moving towards
19 removing the label "spoons" from those and just
20 going to milliliters? This is a really serious
21 issue, and I know about it because I use a lot of
22 very, very toxic drugs. So this is a huge worry.

1 DR. KOCHANOWSKI: We do, as part of our
2 voluntary guidelines, strongly encourage using
3 milliliter only. Milliliter is the primary
4 measure, and many of the manufacturers are
5 converting now to milliliter only. You'll
6 certainly see that with a lot of the infant
7 products.

8 If someone wants to label in spoons, we've
9 suggested only teaspoon, abbreviated a certain way,
10 no tablespoons, and there is a difference of
11 opinion right now as to whether spoons can be
12 dropped completely tomorrow versus phasing that
13 out. But we would certainly like to encourage
14 everyone to just go to milliliter.

15 DR. NEILL: Thanks very much. So having no
16 other names on my list, we will conclude today. I
17 think we've had a lot of good questions. I have
18 some homework for the committee members that
19 includes reviewing the language of the questions.
20 The work of the group tomorrow will be to try and
21 provide the staff with considered opinion and some
22 votes on these questions. And so if you look

1 specifically, I think a lot of the questions that
2 we've discussed today speak to some of the very
3 specific issues, and I'm hopeful that we'll have
4 some more opportunity for some give-and-take
5 revolving around the specific questions tomorrow.

6 **Adjournment**

7 Before you leave today, make sure and take
8 all of your belongings, including your notes, your
9 agenda book, any of your personal belongings. The
10 room tonight will be essentially emptied and
11 cleaned so that you can come back in tomorrow to a
12 nice, fresh, maybe even warmer room to meet in.

13 Thanks very much. We are adjourned.

14 [Pause.]

15 DR. NEILL: I'm reminded that all committee
16 members should please refrain from discussing the
17 topics under consideration at today's meeting
18 either with members or members of the public until
19 we reconvene tomorrow morning. Thank you.

20 We're now adjourned.

21 (Whereupon, at 4:54 p.m., the meeting was
22 adjourned.)