



U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. This content has not been altered or updated since it was archived.

1 FOOD AND DRUG ADMINISTRATION (FDA)
2 CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
3 JOINT MEETING OF THE
4 DRUG SAFETY AND RISK MANAGEMENT ADVISORY
5 COMMITTEE, NONPRESCRIPTION DRUGS ADVISORY
6 COMMITTEE AND THE ANESTHETIC AND LIFE
7 SUPPORT DRUGS ADVISORY COMMITTEE
8 MEETING TO ADDRESS THE PUBLIC HEALTH PROBLEM
9 OF LIVER INJURY RELATED TO THE USE OF
10 ACETAMINOPHEN IN BOTH OVER-THE-COUNTER AND
11 PRESCRIPTION PRODUCTS
12

13 JUNE 29, 2009

14 8:00 a.m.
15
16
17

18 MARRIOTT CONFERENCE CENTERS
19 UNIVERSITY OF MARYLAND, UNIVERSITY COLLEGE
20 UMUC INN AND CONFERENCE CENTER
21 3501 UNIVERSITY BOULEVARD EAST
22 ADELPHI, MARYLAND

1 DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

2 MEMBERS (VOTING):

3 SUSAN R. HECKBERT, M.D., Ph.D.

4 Professor of Epidemiology

5 University of Washington Cardiovascular

6 Health Research Unit

7 Metropolitan Park East, Suite 1360

8 1730 Minor Avenue

9 Seattle, Washington 98101

10
11 JUDITH M. KRAMER, M.D., M.S.

12 Associate Professor of Medicine

13 Duke University Medical Center

14 24000 Pratt Street

15 Room 0311 Terrace Level

16 Durham, North Carolina 27705

17
18 SIDNEY M. WOLFE, M.D.

19 Director, Health Research Group of Public

20 Citizen

21 1600 20th Street, N.W.

22 Washington, D.C. 20009

1 CONSULTANTS (TEMPORARY VOTING)

2 WILLIAM COOPER, M.D.

3 Professor of Pediatrics and Preventive

4 Medicine

5 Vanderbilt University

6 AA-0216 MCN

7 Nashville, Tennessee 37232

8
9 RUTH S. DAY

10 Director, Medical Cognition Laboratory

11 Duke University

12 Durham, North Carolina 27708

13
14 EDWARD KRENZELOCK, Pharm.D.

15 Director, Pittsburgh Poison Center

16 University of Pittsburgh Medical Center

17 Birmingham Towers, Suite 720

18 2100 Wharton Street

19 Pittsburgh, Pennsylvania 15203

20

21

22

1 ELAINE MORRATO, Dr.P.H.D.
2 Assistant Professor, Department of
3 Pediatrics
4 University of Colorado
5 12477 East 19th Avenue
6 Building 406, Room T09-105
7 Aurora, Colorado 80045

8
9 LEWIS NELSON, M.D. (Acting Chair)
10 Director, Fellowship in Medical
11 Toxicology
12 New York University School of Medicine
13 455 First Avenue, Room 123
14 New York, New York 10016

15
16 ANDY STERGACHIS, Ph.D., R.Ph.
17 Professor of Epidemiology and Global
18 Health
19 School of Public Health, University of
20 Washington
21 1107 NE 45th Street
22 Seattle, Washington 98105

1 ALLEN VAIDA, Pharm.D.
2 Executive Vice President
3 Institute for Safe Medication Practices
4 200 Lakeside Drive, Suite 200
5 Horsham, Pennsylvania 19044

6 NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS
7 (VOTING):

8 NEAL L. BENOWITZ, M.D.
9 Professor, Departments of Medicine and
10 Biopharmaceutical Science
11 University of California San Francisco
12 P.O. Box 1220
13 San Francisco, California 94143

14
15 JANET P. ENGLE, Pharm.D., FAPhA
16 Executive Associate Dean and Head
17 Department of Pharmacy Practice
18 College of Pharmacy
19 University of Illinois at Chicago
20 833 South Wood Street
21 M/C 886, Suite 166
22 Chicago, Illinois 60612

1 NEIL J. FARBER, M.D.

2 Professor of Clinical Medicine

3 University of California San Diego

4 8939 Villa La Jolla Drive, Suite 110

5 La Jolla, California 92037

6
7 WALID F. GELLAD, M.D., M.P.H.

8 Assistant Professor of Medicine

9 Center for Health Equity Research and

10 Promotion

11 VA Pittsburgh Health System

12 7180 Highland Drive

13 Pittsburgh, Pennsylvania 15206

14
15 MARIE R. GRIFFIN, M.D.

16 Professor, Department of Preventive

17 Medicine

18 Vanderbilt University Medical Center

19 1500 21st Avenue, Suite 2600

20 Nashville, Tennessee 37232

21

22

1 RENE E R. JENKINS, M.D.
2 Professor and Chair, Department of
3 Pediatrics and Child Health
4 Howard University College of Medicine
5 HURBI Building
6 1840 7th Street, N.W., Room 214
7 Washington, D.C. 20060

8
9 WINIFRED A. LANDIS, R.Ph., C.D.E.
10 CVS Pharmacy 6677
11 3630 South 18th Street
12 Lafayette, Indiana 47909

13
14 WILLIAM H. SHRANK, M.D., M.S.H.S.
15 Instructor, Division of
16 Pharmacoe pidemiology and
17 Pharmacoeconomics
18 Brigham and Women's Hospital
19 Harvard Medical School
20 1620 Tremont Street, Suite 3030
21 Boston, Massachusetts 02120
22

1 LESLIE R. WALKER-HARDING, M.D.
2 Chief, Adolescent Medicine Section
3 Children's Hospital and Regional Medical
4 Center
5 4800 Sand Point Way, N.E.
6 Seattle, Washington 98105

7
8 DORRAINE D. WATTS, Ph.D., R.N.
9 Associate Professor, Graduate School of
10 Nursing, Uniformed Services University of
11 the Health Sciences
12 4301 Jones Bridge Road
13 Bethesda, Maryland 20814

14 CONSULTANT (NON-VOTING):

15 LORNA C. TOTMAN, Ph.D., DABT
16 Acting Industry Representative
17 Lorna Totman Consulting, LLC
18 8409 Frost Way
19 Annandale, Virginia 22003

1 ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY

2 COMMITTEE MEMBERS (VOTING):

3 SORIN J. BRULL, M.D.

4 Professor and Consultant

5 Mayo Clinic College of Medicine

6 Department of Anesthesiology

7 4500 San Pablo Road

8 Jacksonville, Florida 32224

9
10 JEFFREY R. KIRSCH, M.D.

11 Professor and Chair, Department of

12 Anesthesiology and Perioperative Medicine

13 Oregon Health and Science University

14 3181 S.W. Sam Jackson Park Road, UHS-2

15 Portland, Oregon 97239

16
17 OSEMWOTA A. OMOIGUI, M.D.

18 Consumer Representative

19 Division of Inflammation and Pain

20 Los Angeles Pain Clinic

21 4019 W. Rosecrans Avenue

22 Hawthorne, California 90250

1 JULIA E. POLLOCK, M.D.
2 Virginia Mason Medical Center
3 Clinical Assistant Professor
4 University of Washington Medical Center
5 Seattle, Washington 98101
6

7 DONALD S. PROUGH, M.D.
8 Professor and Chairman, Department of
9 Anesthesiology
10 University of Texas
11 Galveston, Texas 77555
12

13 DANIEL ZELTERMAN, Ph.D.
14 Professor and Acting Division Head
15 Division of Biostatistics, Epidemiology
16 and Public Health
17 Yale University School of Medicine
18 New Haven, Connecticut 06520
19
20
21
22

1 CONSULTANTS (TEMPORARY VOTING):

2 EDWARD COVINGTON, M.D.

3 Chronic Pain Rehabilitation Program, C-21

4 Cleveland Clinic Foundation

5 9500 Euclid Avenue

6 Cleveland, Ohio 44195

7
8 RICHARD DeNISCO, M.D., M.P.H.

9 Medical Officer, NIH/NIDA

10 6001 Executive Boulevard

11 Room 5158, MSC 9589

12 Bethesda, Maryland 20852

13
14 JAMES EISENACH, M.D.

15 Professor of Anesthesiology

16 Wake Forest University Medical Center

17 Medical Center Boulevard

18 Winston-Salem, North Carolina 27157

19

20

21

22

1 ROBERT D. KERNS, Ph.D.
2 Professor of Psychiatry, Neurology and
3 Psychology
4 Yale University
5 VA Connecticut Healthcare System
6 West Haven, Connecticut 06516
7

8 KARL LORENZ, M.D., M.S.H.S.
9 VA Greater Los Angeles Healthcare System
10 Division of General Internal Medicine,
11 Code 111-G
12 Los Angeles, California 90073
13

14 JOHN MARKMAN, M.D.
15 Director, Translational Pain Research
16 University of Rochester Medical Center
17 601 Elmwood Avenue, Box 670
18 Rochester, New York 14642
19
20
21
22

1 SRINIVASA RAJA, M.D.
2 Professor, Department of
3 Anesthesiology/Critical Care Medicine
4 Division of Pain Medicine
5 Johns Hopkins University
6 600 North Wolfe Street/Osler 292
7 Baltimore, Maryland 21287
8

9 KNOX H. TODD, M.D., M.P.H.
10 Pain and Emergency Medicine Institute
11 Beth Israel Medical Center
12 First Avenue at 16th Street
13 New York, New York 10003
14

15 CONSULTANT (NON-VOTING):

16 CHARLES H. McLESKEY, M.D.
17 Acting Industry Representative
18 Global Anesthesia and Critical Care
19 Baxter Healthcare Corporation
20 95 Spring Street
21 New Providence, New Jersey 07974
22

1 CDER CONSULTANTS (TEMPORARY VOTING):

2 MARIO CHOJKIER, M.D.

3 Professor of Medicine

4 University of California San Diego

5 3350 La Jolla Village Drive, Room 111-D

6 San Diego, California 92161

7
8 MARILYN EICHNER

9 Patient Representative

10 Rockville, Maryland 20853

11
12 ROBERT LEVINE, M.D.

13 Professor of Medicine

14 SUNY Upstate Medical University

15 State University Hospital

16 750 East Adams Street

17 Syracuse, New York 13210

18
19
20
21
22

1 NANCY J. OLSEN, M.D.
2 Professor of Internal Medicine
3 University of Texas Southwestern Medical
4 School
5 5323 Harry Hines Boulevard
6 Dallas, Texas 75390

7 FDA (NON-VOTING):

8 SANDRA L. KWEDER, M.E.
9 Deputy Director, Office of New Drugs
10

11 CHARLES GANLEY, M.D.
12 Director Office of Nonprescription
13 Products
14

15 GERALD DAL PAN, M.D., M.H.S.
16 Director, Office of Surveillance and
17 Epidemiology
18

19 SHARON HERTZ, M.D.
20 Deputy Director, Division of Anesthesia,
21 Analgesia, Rheumatology Products
22

1 GUEST SPEAKERS (NON-VOTING):

2 WILLIAM BOWER, M.D., F.I.D.S.A.

3 Command, U.S. Public Health Service

4 Office of Blood, Organ and Other Tissue

5 Safety

6 Centers for Disease Control and

7 Prevention

8 1600 Clifton Road

9 Atlanta, Georgia 30333

10
11 DANIEL S. BUDNITZ, M.D., MPH, CDR, USPHS

12 Division of Healthcare Quality Promotion,

13 CDC

14 1600 Clifton Road, N.E., Mailstop A-24

15 Atlanta, Georgia 30333

16
17
18
19
20
21
22

1 PAUL DARGAN, M.B.B.S., FRCPE, FACMT

2 Consultant Physician and Clinical

3 Toxicologist

4 Clinical Director for Toxicology

5 2nd Floor Bermondsey Wing

6 Guy's Hospital

7 Great Maze Pond, London, SE1 9RT, UK

8
9 KEITH HAWTON, D.Sc, D.M. (via telephone)

10 Director for Suicide Research

11 University Department of Psychiatry

12 Warneford Hospital

13 Oxford, OX3 7JX

14
15 LAURA JAMES, M.D.

16 Section of Pediatric Pharmacology and

17 Toxicology

18 Sturgis 3114

19 Arkansas Children's Hospital

20 800 Marshall Street

21 Little Rock, Arkansas 72202

22

1 WILLIAM LEE, M.D.

2 Meredith Mosle Chair in Liver Diseases

3 UT Southwestern Medical Center

4 5959 Harry Hines Boulevard

5 Dallas, Texas 75390

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

I N D E X

AGENDA ITEM	PAGE
Introductory remarks	
Lewis Nelson, M.D.	23
Conflict of interest statement	
Elaine Ferguson, MS	25
Introduction of the committee	
Lewis Nelson, M.D.	31
FDA presentation	
Acetaminophen Background and Overview	
Gerald Dal Pan, M.D.	37
FDA Regulatory Information	
Regulation of Acetaminophen Drug Products	
Arlene Solbeck, MS	45
FDA Marketing Information	
OTC and Rx Acetaminophen Market Overview	
Laura Governale, Pharm.D.	57
Metabolism/Toxicology Background	
Laura James, M.D.	69
Committee Questions	89
Consumer Healthcare Products Association	
Linda Suydam, DPA	100

1	AGENDA ITEM	PAGE
2	James H. Lewis, M.D.	113
3	Denver Health: The Safety of Acetaminophen	
4	During Therapeutic Use	
5	Richard C. Dart, M.D.	129
6	McNeil Consumer Healthcare	
7	Introduction and McNeil Position	
8	Edwin Kuffner, M.D.	146
9	Acetaminophen Efficacy Among Doses	
10	Cathy Gelotte, Ph.D.	154
11	Proposed Risk Mitigation Framework Based	
12	on Root Cause Analysis	
13	Edwin Kuffner, M.D.	168
14	Epidemiologic-Based Switching Model	
15	Kenneth Rothman, DrPh	187
16	Cadence Sponsor Presentation	
17	James B. Breitmeyer, M.D.	198
18	Committee Questions	211
19	Safety Update on ALF Study Group	
20	William Lee, M.D.	235

21
22

1	AGENDA ITEM	PAGE
2	Acetaminophen-Related Emergency Department	
3	Visits - Findings from NEISS 2004-2007	
4	Dan Budnitz, M.D., MPH, CDR, USPHS	260
5	CDC Data: ALF and Acetaminophen	
6	William Bower, MD, FIDSA, CDR, UPHS	277
7	FDA Data: Characterization of Acetaminophen	
8	Overdose and Related Hepatotoxic Events	
9	Angelika Manthripragada, Ph.D.	285
10	Committee Questions	302
11	Single-Ingredient Acetaminophen Dose-Response	
12	Data in Adults	
13	Christina Chang, M.D.	323
14	Rx Acetaminophen Combination Products	
15	Jane Filie, M.D.	341
16	Education Outreach: FDA Consumer Education	
17	on the Safe Use of Acetaminophen	
18	Ellen Frank	354
19	OTC Use Behavior: Comprehension and	
20	Behavioral Factors Associated With OTC	
21	Medication Misuse	
22	Laura Shay, Ph.D.	364

1	AGENDA ITEM	PAGE
2	Open Public Hearing	383
3	Committee Questions	419
4	Adjournment	443

5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

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

2 - - - - -

3 DR. NELSON: Welcome, everybody. My name
4 is Lewis Nelson, and I'm an emergency physician
5 and medical toxicologist from New York University
6 School of Medicine, and I'm chairing this advisory
7 committee, or this joint advisory committee, which
8 is on acetaminophen toxicity. It's a joint
9 meeting of the drug safety and risk management
10 advisory committee, the nonprescription drugs
11 advisory committee, and the anesthetic and life
12 support drugs advisory committee.

13 As you know, it's a fairly long meeting,
14 and quite packed, and I'm going to do my best to
15 try to keep us moving and on time, and focused on
16 the issues at hand.

17 So before we get started, I'd just like
18 to read some introductory remarks.

19 For topics such as those being discussed
20 at today's meeting, there are often a variety of
21 opinions, some of which are quite strongly held.
22 Our goal is that today's meeting will be a fair

1 and open forum for discussion of these issues and
2 that individuals can express their views without
3 interruption. Thus, as a gentle reminder,
4 individuals will be allowed to speak into the
5 record only if recognized by the chair.

6 In the spirit of the Federal Advisory
7 Committees Act and the Government in the Sunshine
8 Act, we ask that the advisory committee members
9 take care that any conversation about today's
10 topic take place in the open forum of the meeting,
11 not during breaks, lunch or, for this meeting,
12 overnight.

13 We are also aware that members of the
14 media are anxious to speak with the FDA about
15 these proceedings; however, like the advisory
16 committee members, FDA will refrain from
17 discussing the details of this meeting with the
18 media until its conclusion. For the convenience
19 of the media representatives, I would like to
20 identify the FDA press contact, Ms. Riley -- if
21 you're in the area, please present yourself.
22 Thank you.

1 And finally, I would like to remind
2 everybody present to please silence your cell
3 phones and pagers if you have not already done so.

4 We look forward to an interesting and
5 productive meeting. Thank you for your
6 participation and cooperation.

7 I would like to next ask Elaine Ferguson,
8 who is next to me, to present the conflict of
9 interest statements.

10 MS. FERGUSON: The Food and Drug
11 Administration, FDA, is convening today's meeting
12 of the drug safety and risk management,
13 nonprescription drugs, and the anesthetic and life
14 support drugs advisory committees of the Center
15 for Drug Evaluation and Research. Under the
16 authority of the Federal Advisory Committee Act of
17 1972, with the exception of the industry
18 representatives, all members and temporary voting
19 members of the committees are special government
20 employees, SGEs, or regular federal employees from
21 other agencies and are subject to federal conflict
22 of interest laws and regulations.

1 The following information on the status
2 of this committee's compliance with federal ethics
3 and conflict of interest laws covered by, but not
4 limited to, those found at 18 USC section 208 and
5 section 712 of the Federal Food, Drug and Cosmetic
6 Act (FD&C Act) is being provided to participants
7 in today's meeting and to the public.

8 FDA has determined that members and the
9 temporary voting members of these committees are
10 in compliance with the federal ethics and conflict
11 of interest laws under 18 USC section 208(b)(3).

12 Congress has authorized FDA to grant
13 waivers to special government employees who have
14 potential financial conflicts when it is
15 determined that the agency's need for a particular
16 individual's service outweighs his or her
17 potential financial conflict of interest.

18 Under USC 208 (b)(1), Congress has
19 authorized FDA to grant waivers to regular
20 government employees who have potential financial
21 conflicts when it is determined that the financial
22 interest is not so substantial to be likely to

1 affect the integrity of the individual's service
2 to the government.

3 Under section 712 of the FD&C Act,
4 Congress has authorized FDA to grant waivers to
5 special and regular government employees with
6 potential financial conflicts when necessary to
7 afford the committee essential expertise.

8 Related to the discussions of today's
9 meeting, members and temporary voting members of
10 these committees who are special and regular
11 government employees have been screened for
12 potential financial conflicts of interest of their
13 own, as well as those imputed to them, including
14 those of their spouses or minor children and, for
15 purposes of 18 USC section 208, their employers.

16 These interests may include investments,
17 consulting, expert witness testimony, contracts,
18 grants, CRADAs, teachings, speaking, writing,
19 patents and royalties and primary employment.

20 For today's agenda, the committees will
21 discuss and make recommendations regarding how to
22 address the public health problem of liver injury

1 related to the use of acetaminophen in both
2 over-the-counter (OTC) and prescription (Rx)
3 products.

4 This is a particular matters meeting
5 during which general issues will be discussed.

6 Based on the agenda and all financial
7 interests reported by the members and temporary
8 voting members of the committees, it has been
9 determined that all interest in firms regulated by
10 the Center for Drug Evaluation and Research
11 present no potential for a conflict of interest.

12 With respect to the FDA's invited
13 industry representative, we would like to disclose
14 that Dr. Lorna Totman and Dr. Charles McLeskey are
15 participating in this meeting as non-voting
16 industry representatives, acting on behalf of
17 regulated industry. Their role at this meeting is
18 to represent industry in general and not any one
19 particular company. Dr. Totman is an independent
20 pharmaceutical consultant, and Dr. McLeske is
21 employed by Baxter Healthcare Corporation.

22 With regard to the FDA's guest speakers,

1 the agency has determined that the information to
2 be provided by the speakers is essential. The
3 following interests are to be made public to allow
4 the audience to objectively evaluate any
5 presentation and/or comments made by the speakers.

6 In January 2009, Dr. Paul Dargan attended
7 an advisory meeting at McNeil Pharmaceuticals and
8 presented a summary of the literature on the
9 impact of the United Kingdom's legislation
10 limiting the pack size of paracetamol
11 (acetaminophen) on poisoning involving paracetamol
12 (acetaminophen). He has no ongoing relationships
13 with McNeil.

14 Dr. Laura James is a co-investigator for
15 three National Institutes for Health-funded
16 studies related to acetaminophen. Dr. James has
17 also performed assays of acetaminophen protein
18 adducts for samples provided by Denver Health, and
19 she was a principal investigator for a
20 pharmacokinetic study of acetaminophen-containing
21 products.

22 As guest speakers, Drs. Dargan and James

1 will not participate in the committee's
2 deliberation, nor will they vote.

3 We would like to remind the members and
4 temporary voting members of the committees that if
5 the discussion involves any other products or
6 firms not already on the agenda for which an FDA
7 participant has a personal or imputed financial
8 interest, the participants need to exclude
9 themselves from such involvement, and their
10 exclusion will be noted for the record.

11 FDA encourages all other participants to
12 advise the committees of any financial
13 relationships that they may have with any firm at
14 issue.

15 At this moment, I'd just like to remind
16 you, this is a very large meeting, so for the
17 purpose of the transcriber, if you can please
18 state your name first into the microphone before
19 you speak, it will be much easier for her to keep
20 track of who has said what. Thank you very much.

21 DR. NELSON: Thank you. Along those
22 lines, it is a fairly large meeting, and I know

1 most of us don't know each other, and it would be
2 great if we could have a brief introduction, just
3 a one line with your name, perhaps starting at the
4 back with Dr. Dal Pan.

5 DR. DAL PAN: Gerald Dal Pan, Office of
6 Surveillance and Epidemiology, CDER, FDA.

7 DR. KWEDER: Good morning. I'm Sandra
8 Kweder. I'm the deputy director of the Office of
9 New Drugs in CDER.

10 DR. GANLEY: Charlie Ganley. I'm the
11 director of the Office of Nonprescription
12 Products.

13 DR. HERTZ: Sharon Hertz. I'm the deputy
14 director of the Division of Anesthesia, Analgesia
15 and Rheumatology Products.

16 DR. KRENZELOK: Good morning. I'm
17 Episode Krenzelok. I'm director of the Pittsburgh
18 Poison Center and a professor of pharmacy and
19 pediatrics at the University of Pittsburgh.

20 DR. WATTS: I'm Dr. Dorraine Watts. I'm
21 with the Uniformed Services University. I'm an
22 associate professor of statistics and research

1 design.

2 DR. COOPER: I'm Bill Cooper, in
3 pediatrics at Vanderbilt University.

4 DR. POLLOCK: I'm Julia Pollock. I'm an
5 anesthesiologist at Virginia Mason Medical Center
6 in Seattle.

7 MS. DAY: Ruth Day. I'm the director of
8 the Medical Cognition Laboratory at Duke
9 University.

10 DR. MARKMAN: John Markman. I'm the
11 director of the Neuromedicine and Pain Management
12 Center at the University of Rochester in
13 Rochester, New York.

14 DR. VAIDA: Allen Vaida. I'm the
15 executive vice president at the Institute for Safe
16 Medication Practices.

17 MS. EICHNER: Marilyn Eichner, patient
18 consultant for the FDA. Thank you.

19 DR. CHOJKIER: Mario Chojkier, professor
20 of medicine, University of California San Diego.

21 DR. ZELTERMAN: I'm Dan Zelterman,
22 professor of biostatistics at Yale University.

1 DR. EISENACH: Jim Eisenach, an
2 anesthesiologist at Wake Forest University.

3 DR. LANDIS: Good morning. Winnie
4 Landis, pharmacist and diabetes educator with CVS
5 in Lafayette, Indiana.

6 DR. COVINGTON: Episode Covington. I'm
7 the director of the Neurological Center for Pain
8 at Cleveland Clinic in Cleveland, Ohio.

9 DR. RAJA: Srinivasa Raja, director of
10 the Division of Pain Medicine at Johns Hopkins
11 University.

12 DR. GRIFFIN: Marie Griffin, internist
13 and pharmacoepidemiologist at Vanderbilt
14 University.

15 DR. BENOWITZ: Neal Benowitz, internist,
16 clinical pharmacologist and medical toxicologist,
17 University of California San Francisco.

18 DR. NELSON: Lewis Nelson from New York
19 University.

20 MS. FERGUSON: Elaine Ferguson,
21 designated federal official.

22 DR. KRAMER: Judith Kramer, pharmacist

1 and internist, associate professor of medicine,
2 Duke University.

3 DR. LORENZ: Karl Lorenz, primary care
4 physician and palliative care physician with the
5 Veterans Administration in Los Angeles.

6 DR. FARBER: Neil Farber. I'm in general
7 internal medicine and professor of clinical
8 medicine at University of California San Diego.

9 DR. KIRSCH: Jeff Kirsch, professor and
10 chair of anesthesiology at Oregon Health Science
11 University.

12 DR. KERNS: Good morning. Bob Kerns.
13 I'm a national program director for pain
14 management for the Department of Veterans Affairs,
15 and I'm a professor of psychiatry, neurology and
16 psychology at Yale University.

17 DR. WALKER-HARDING: Leslie
18 Walker-Harding. I am the chief of the Division of
19 Adolescent Medicine at the University of
20 Washington and Seattle Children's, and associate
21 professor in the Department of Pediatrics.

22 DR. PROUGH: Don Prough. I'm the chair

1 of anesthesiology at the University of Texas in
2 Galveston.

3 DR. MORRATO: Elaine Morrato. I'm
4 associate director of our children's outcomes
5 research program at the Children's Hospital in
6 Denver, and an epidemiologist in the departments
7 of pediatrics, clinical pharmacy.

8 DR. ENGLE: I'm Jan Engle. I'm a
9 pharmacist. I'm the executive associate dean and
10 professor and head of pharmacy practice at
11 University of Illinois at Chicago.

12 DR. LEVINE: Good morning. I'm Bob
13 Levine, professor of medicine and chief of
14 hepatology, State University of New York, Upstate
15 Medical University, Syracuse, New York.

16 DR. TODD: I'm Knox Todd. I'm professor
17 of emergency medicine at Albert Einstein College
18 of Medicine, and I direct the Pain and Emergency
19 Medicine Institute at Beth Israel Medical Center
20 in Manhattan.

21 DR. OMOGUI: Sota Omogui, anesthesiology
22 and pain, L.A. Pain Clinic, Hawthorne, California.

1 DR. OLSEN: Nancy Olsen. I'm a
2 rheumatologist at University of Texas Southwestern
3 Medical Center in Dallas.

4 DR. HECKBERT: Susan Heckbert. I'm a
5 general internist and pharmacoepidemiologist at
6 the University of Washington.

7 DR. BRULL: I'm Sorin Brull. I'm
8 professor of anesthesiology at the Mayo Clinic
9 College of Medicine, consultant at -- in
10 Jacksonville.

11 DR. STERGACHIS: Andy Stergachis,
12 professor of epidemiology and global health, and
13 pharmacist, University of Washington.

14 DR. SHRANK: Will Shrank. I'm an
15 internist in the Division of Pharmacoepidemiology
16 and Pharmacoeconomics at Brigham and Women's
17 Hospital.

18 DR. WOLFE: Sid Wolfe. I'm an internist
19 and director of the health research group at
20 Public Citizen.

21 DR. GELLAD: Walid Gellad. I'm a primary
22 care doctor and assistant professor of medicine at

1 the University of Pittsburgh and the Pittsburgh
2 VA.

3 DR. MCLESKEY: Charlie McLeskey,
4 anesthesiologist by training, currently working at
5 Baxter, and the acting industry rep for ALSDAC.

6 DR. TOTMAN: Lorna Totman, a
7 pharmacologist, toxicologist and the industry
8 representative to NDAC.

9 DR. NELSON: Well, thank you very much,
10 everybody. Welcome. I'd like to now ask
11 Dr. Dal Pan to come up and make his introductory
12 remarks and provide some background. Dr. Dal Pan
13 is the director of the Office of Surveillance and
14 Epidemiology, as you heard, at CDER.

15 DR. DAL PAN: Good morning, and thank
16 you. As Dr. Nelson said, I'm Gerald Dal Pan. I'm
17 the director of the Office of Surveillance and
18 Epidemiology at FDA's Center for Drug Evaluation
19 and Research, and I'd like to welcome all the
20 members of the three committees that are here
21 today, as well as the guest speakers and other
22 guests to this two-day meeting.

1 We've convened this meeting to discuss
2 specific steps that FDA may take to mitigate liver
3 damage associated with acetaminophen use.

4 Acetaminophen is one of the most widely
5 used medicines in the United States. It's used
6 for the treatment of pain and fever and is found
7 in many prescription and over-the-counter
8 preparations. About 25 billion doses were sold in
9 2008.

10 Acetaminophen is safe and effective when
11 used according to the directions in its
12 over-the-counter and prescription labeling. It's
13 also known commonly as APAP and paracetamol in
14 some other countries.

15 Acetaminophen-induced liver disease is an
16 important and persistent public health problem.
17 In general, as you'll hear over the next day or
18 so, it's usually related to exceeding the maximum
19 daily dose of 4 grams per day. Overdoses can be
20 both unintentional as well as intentional, and
21 this can occur with both over-the-counter and
22 prescription preparations.

1 It's well known that acetaminophen is a
2 leading cause of drug-induced liver injury. In
3 one multi-center study that you'll hear about more
4 over the course of the meeting, it accounted for
5 about half of liver failure cases. In another CDC
6 estimate which, again, you'll hear about, there
7 were about 1600 cases of liver failure of all
8 etiologies in the United States, and acetaminophen
9 was the most common etiology amongst these.
10 You'll hear more about these studies over the next
11 two days.

12 FDA has been actively engaged in this
13 area for several years. A final rule in 1998
14 added warnings about alcohol to the labels of
15 over-the-counter products. You'll hear more about
16 the regulatory framework of over-the-counter
17 products and acetaminophen regulation later this
18 morning.

19 In 2002, FDA convened an advisory
20 committee to focus on unintentional overdose of
21 acetaminophen. The recommendations -- what's
22 happening here? Well, I can still talk even if

1 there's not a slide, I guess.

2 The recommendations from that meeting
3 were that we add a specific liver toxicity
4 warning, that there be distinctive
5 over-the-counter labeling to more readily identify
6 acetaminophen as an ingredient, and a campaign to
7 educate consumers and healthcare professionals
8 about the potential for liver injury.

9 In addition, there were FDA-initiated
10 outreach efforts. In 2004, FDA initiated an
11 educational campaign, the goal of which was the
12 safe use of both non-steroidals and acetaminophen.
13 You'll hear more about this campaign later.

14 As well in 2004, FDA contacted state
15 boards of pharmacy asking that prescriptions use
16 the term "acetaminophen" itself and not APAP. In
17 addition, we asked that they instruct patients not
18 to exceed the maximum recommended daily dose and
19 to avoid drinking alcohol during prescription
20 acetaminophen use.

21 To the best of our knowledge, these
22 recommendations and suggestions have not been

1 implemented.

2 More recently, CDER formed a working
3 group to review safety issues related to
4 acetaminophen and to consider additional steps to
5 reduce acetaminophen-related liver injury. And
6 the need for a public discussion of any
7 intervention was recognized, and today's advisory
8 committee represents that public discussion.

9 Finally, earlier this year a final rule
10 for over-the-counter acetaminophen labeling was
11 issued. This rule strengthened liver-related
12 warnings, ensured that the ingredient name,
13 acetaminophen, is more prominent, and added a
14 warning to avoid other acetaminophen-containing
15 products.

16 So what are the main issues today? The
17 main issue for discussion over the next two days
18 is, what specific steps can be taken to reduce
19 acetaminophen-related liver injury? FDA will
20 present a series of options for discussion today
21 and tomorrow. FDA is considering these options,
22 but has not decided on any one of them. We're

1 seeking your input on these options, and we're
2 open to hearing other options as well.

3 It's important to understand that this
4 meeting is focused on options for minimizing
5 acetaminophen-induced liver injury. There are
6 many other aspects of pain treatment, such as the
7 use of opioids and use of nonsteroidal
8 anti-inflammatory agents that are important but
9 aren't the subject of this meeting. As many of
10 you know, we have held a series of meetings on
11 possible steps we can take to mitigate the risks
12 of opioids, and we're busy in this area, but the
13 focus for these two days is acetaminophen.

14 So as you look toward the options, as you
15 consider the options, here are some things to
16 think about as you look at each one of them.
17 What's the potential of this option to decrease
18 the incidence of liver injury? What effect will
19 it have on patients? What effect will it have on
20 healthcare practitioners? What resources may be
21 necessary to implement it? What are the steps
22 that manufacturers may need to take to implement

1 it? What might other potential consequences be?
2 And, importantly in your mind, how would you
3 prioritize each of these options?

4 Let me talk a minute about putting the
5 options into context. The safe use of
6 acetaminophen, really like the safe use of any
7 medicine, requires the engagement of all involved
8 parties: The patients, the prescribers, the
9 pharmacists, the regulators and the industry. And
10 regulatory action may be needed and important, but
11 it will not be sufficient. We really need to
12 engage all the stakeholders in the safe use of
13 this product.

14 So here's an overview of the options.
15 Again, you'll hear more about these later.

16 Option 1 is to reduce the current doses,
17 for example, the current maximum adult daily dose,
18 the single adult daily dose and the tablet
19 strength, or restrict the current maximum adult
20 daily dose, single adult dose and tablet strength
21 the prescription status only.

22 Option 2 is to establish package size

1 limits for over-the-counter acetaminophen
2 products.

3 Option 3 is to require unit-of-use
4 packaging for prescription products.

5 Option 4 is to expand the product warning
6 information on prescription products.

7 Option 5 is eliminate combination
8 over-the-counter or prescription products that
9 contain acetaminophen.

10 And option 6 is to limit dosing
11 formulations for over-the-counter liquid products
12 and to require dosing devices.

13 Again, you'll hear more about these, but
14 keep these in mind as you listen to the
15 presentations throughout the course of the day.

16 This is a very busy meeting. We have two
17 full days here, and the first day is largely
18 presentations. You'll hear from FDA and FDA's
19 invited speakers, speaking about regulatory status
20 of how this medicine is regulated, marketing and
21 usage information, information on metabolism and
22 toxicology, information on drug safety, efficacy,

1 over-the-counter usage, educational efforts, and
2 some experience from the United Kingdom where
3 they've taken specific steps to address this issue
4 as well. You'll also hear a presentation from
5 industry.

6 On each day we'll have two -- we'll have
7 one hour each, on each of the two days, of an open
8 public hearing, and much of the second day,
9 tomorrow, will be devoted to your discussion and,
10 finally, voting.

11 So, with that, I once again welcome you,
12 thank you for coming here to help us with this.
13 And over the next -- over today you'll really be
14 hearing a lot more details about everything I
15 spoke about. Thank you.

16 DR. NELSON: I'm sorry. I will introduce
17 you. I assumed you were going to just follow
18 Dr. Dal Pan.

19 This is Arlene Solbeck from the Division
20 of Nonprescription Regulation Development in the
21 Office of Nonprescription Products.

22 MS. SOLBECK: Good morning. My name is

1 Arlene Solbeck, a regulatory review scientist in
2 the Division of Nonprescription Regulation
3 Development, and this morning I'm going to discuss
4 the regulation of acetaminophen drug products.

5 Acetaminophen is available to consumers
6 in many OTC and prescription products. I'm going
7 to briefly explain the regulatory mechanisms for
8 marketing acetaminophen drugs with the primary
9 focus on the OTC monograph. Then I'm going to
10 review some regulatory history for OTC
11 acetaminophen, primarily focusing on the new
12 labeling requirements to address the health
13 problem of liver injury related to acetaminophen
14 use.

15 First, regulatory mechanisms. The
16 submission of NDAs, which are new drug
17 applications, and abbreviated NDAs for generic
18 drugs are the regulatory mechanisms to market all
19 prescription and some OTC drugs, and some OTC
20 drugs that are regulated under an NDA would be the
21 suppository form of acetaminophen and the extended
22 release dose of acetaminophen.

1 What is important to remember here about
2 the NDA process is that, when FDA approves a drug
3 under an NDA or an ANDA, it is specific for that
4 single drug product under application. It is drug
5 product-specific. And changes to the NDA require
6 FDA's preapproval, and there are also mandated
7 timelines for the review process.

8 Now, this is a slide on prescription
9 combination products. All prescription
10 combination products are combination products.
11 This table shows the different ingredients,
12 particularly the opioid ingredients, that are
13 combined with acetaminophen and available by
14 prescription. Combination products with opioids
15 account for the majority of prescription
16 acetaminophen products combination products in the
17 marketplace, and the doses range from 325 to 350
18 [sic] milligrams acetaminophen per tablet for
19 single doses of 325 to 1,000 milligrams
20 acetaminophen. And there will be other speakers
21 this morning speaking on the prescription
22 acetaminophen.

1 So now let's move to the OTC monograph.
2 Certain OTC drugs that were on the market prior to
3 1972 are part of a rulemaking known as the OTC
4 drug review. And so rather than review each drug
5 product individually, a review process was set up
6 known as the OTC drug review to review categories
7 of ingredients. And the data on the safety and
8 the efficacy of ingredients for these categories
9 were collected through public notice and comment.

10 So what's important to remember about the
11 monograph process is that it is a multi-step
12 rulemaking process requiring public notice and
13 comment and it is category-specific.

14 OTC monographs establish conditions for
15 use for ingredients determined to be generally
16 recognized as safe and effective, and
17 manufacturers follow conditions of use outlined in
18 the monograph for marketing so that no preapproval
19 is required. So, therefore, when FDA approves a
20 drug under an NDA, we say it's approved. Under
21 the OTC monograph, we say that the drug product is
22 generally recognized as safe and effective if the

1 manufacturer follows the conditions that are
2 outlined under the monograph.

3 Most OTC acetaminophen products are
4 marketed under the OTC monograph.

5 These are some steps in the rulemaking
6 process. It's a multi-step rulemaking process.
7 Monograph starts with an ANPR, which is the
8 advanced notice of proposed rulemaking, and a
9 review of active ingredients by an external review
10 or an advisory review board. Then there's a
11 proposed rule, FDA's stated position on the safety
12 and effectiveness of the ingredients being under
13 review, and finally the final rule, FDA's final
14 conclusions on the safety and the efficacy of the
15 ingredients being reviewed and defines conditions
16 under which ingredients are generally recognized
17 as safe and effective.

18 So I point out that between each
19 rulemaking is a public comment period, and the
20 timeline for collecting comments and data and
21 publishing a subsequent rulemaking could take
22 years. For acetaminophen, we're at the proposed

1 rule of rulemaking, although we have finalized
2 some parts of the proposed rule concerning the
3 runnings, which I'm going to discuss in a few
4 minutes. But it's important here to say that any
5 recommendation coming out of this committee that
6 will require some rulemaking activity, we will be
7 starting with the proposed rule, and then we will
8 need a final rule to put that into action.

9 And now some regulatory events.

10 Acetaminophen rulemaking started with the advanced
11 notice of proposed rulemaking in 1977, and then a
12 proposed rule was published in 1988. The 1988
13 proposed rule established the initial conditions
14 for marketing, including the safe and effective
15 dosage strengths, the indications for use, and all
16 the various combinations of OTC products that can
17 be combined with acetaminophen.

18 This table summarizes the dosage schedule
19 for solid oral dosage forms for adults from the
20 1988 proposed rule. A 325-milligram dosage form
21 and a 500-milligram dosage form are under the
22 monograph, and an additional 650 dosage form is

1 currently marketed under an NDA. However, all
2 three -- for all three, the 24-hour maximum daily
3 dosage is 4,000 grams [sic].

4 And this table shows a slide for all the
5 OTC ingredients that can be combined with
6 acetaminophen in accordance with our 1988 proposed
7 rule. These combination products come in a wide
8 range of doses for a variety of different
9 indications, and so occupy a significant number of
10 products in the marketplace.

11 So after our 1988 proposed rule, there
12 were several rulemakings and advisory committee
13 meetings that addressed unintentional liver injury
14 and our shown on this table. First, in 1993, we
15 had an advisory committee meeting discussing
16 alcohol use and abuse with the use of
17 acetaminophen, and this led to a 1997 proposed
18 rule and a published final rule by FDA requiring
19 an alcohol warning because of the recognition that
20 heavy alcohol use or abuse is a risk factor for
21 liver injury with acetaminophen.

22 Next, we had a 2002 advisory committee

1 where we discussed the need for a liver warning
2 and other labeling issues.

3 And following that meeting we began, in
4 2004, a public information campaign, and this led
5 to a publication of a proposed rule in 2006 where
6 we proposed important liver injury warning
7 language in 2006. And this 2006 proposed rule was
8 finalized in 2009. And I'm going to focus on that
9 for the rest of the presentation.

10 However, before moving on to the required
11 labeling, I did want to mention that we received
12 some submissions suggesting additions to prevent
13 acetaminophen liver injury just prior to the
14 publication of the 2006 proposed rule for the
15 liver warning.

16 For example, we received this citizens'
17 petition PPSI, which stands for Pharmacists'
18 Planning Service, Incorporated -- we received it
19 in 2006, right before we published our proposed
20 rule, and besides the labeling requirements, which
21 the petitioner has asked for, he is requesting
22 behind-the-counter status of OTC acetaminophen,

1 some package size and type restrictions, as well
2 as some prescription labeling. And we have been
3 able to address the OTC labeling issues from this
4 petition in our recent rulemaking.

5 So what is now required for OTC
6 acetaminophen drug products based on our 2009
7 proposed rule? Well, this is a mock-up of the
8 front of a carton. We refer to it as a principal
9 display panel, or a PDP. And what's required here
10 is that the ingredient name, acetaminophen, must
11 appear as highlighted or bolded. And it must
12 appear in a prominent size. And what we call by
13 prominent size is about one-quarter the size of
14 the largest type on the front of a carton which,
15 generally speaking, is the brand name.

16 And we also are requiring a "see new
17 warnings" information statement on the front of
18 the carton for one year from the date the final
19 rule becomes effective. I've listed the
20 requirements here so that you can use them later
21 on, if you need to, in your future deliberations.

22 What is required for a combination

1 product? Well, basically, the same requirements,
2 except one additional requirement. First of all,
3 the ingredient name acetaminophen must be
4 highlighted or bolded -- must appear. But, in
5 addition, all the names of the ingredients in the
6 combination have to appear.

7 And this is different and significant now
8 because, prior to our rule now, only NSAIDs and
9 acetaminophen are required to present all the
10 information of what is required in the front of a
11 carton -- and all the drugs have to be there, and
12 this is only for NSAIDs and acetaminophen. And
13 the "see new warnings" information also has to be
14 there too.

15 So this is a combination -- I mean, this
16 is a slide showing the labeled warnings based on
17 the 2009 final rule which are required to appear
18 in Drug Facts. This is FDA's standard Drug Facts
19 label. This illustration is for a single
20 ingredient adult acetaminophen product, and so
21 here are the requirements.

22 First, it is voluntary whether a

1 manufacturer wants to highlight the ingredient
2 name or the purpose. For this illustration, we do
3 show it highlighted.

4 Second, there has to be a new liver
5 warning which is required. It states that severe
6 liver damage can occur if you exceed the maximum
7 daily dose, if you use with other drugs containing
8 acetaminophen, or if you drink more than three
9 alcoholic drinks a day while using the product.

10 And so what we've done is we've managed
11 to incorporate the older liver warning into the
12 liver warning that was required for all OTC drug
13 products for adults.

14 Third, we're requiring a separate warning
15 not to use with any other drug containing
16 acetaminophen. And this is to reinforce, once
17 again, that we do not want concomitant use of
18 acetaminophen drugs.

19 And, fourth, ask a doctor before use if
20 you have liver damage. So these are our required
21 language from our 2009 proposed rule.

22 So, in summary, I want to leave with the

1 following points. Prescription acetaminophen
2 products are regulated under NDAs and ANDAs, and
3 all prescription acetaminophen products are
4 combination products.

5 Most acetaminophen OTC products are
6 regulated under the OTC monograph.

7 The 1988 proposed rule which,
8 importantly, is not yet final, establishes the
9 maximum daily dose for adults as 4,000 grams, and
10 various combinations of OTC combinations.

11 Our 2009 liver warning final rule
12 addresses important safety issues for the safe use
13 of acetaminophen. Easier recognition of
14 acetaminophen as an ingredient in a product, and
15 provides awareness of liver injury risk to
16 consumers.

17 And, finally, changes to the current 1998
18 [sic] acetaminophen proposed rule will require a
19 proposed rule followed by a final rule. And I
20 thank you for your attention.

21 DR. NELSON: Thank you. Our next speaker
22 will be Dr. Laura Governale from the Office of

1 Surveillance and Epidemiology, to discuss
2 marketing information concerning acetaminophen.

3 DR. GOVERNALE: Good morning. My name is
4 Laura Governale from the Division of Epidemiology
5 in the Office of Surveillance and Epidemiology.
6 This morning I will be presenting an overview of
7 the over-the-counter and prescription
8 acetaminophen market from years 2004 to 2008.

9 The following is an outline of my
10 presentation. First I will begin with an overview
11 of the overall acetaminophen products sales and
12 then move on to a more detailed analysis of the
13 over-the-counter acetaminophen product sales, and
14 then follow with an analysis of the prescription
15 combination acetaminophen market through dispensed
16 prescription analysis. Then I will wrap up with a
17 summary of my presentation.

18 Before I present the results of each
19 analysis, I want to provide an overview of the
20 databases that were used in each of these
21 analyses. For the national over-the-counter
22 prescription trend, it was obtained from the IMS

1 Health National Sales Perspectives. This database
2 measures the volume of prescription and
3 over-the-counter products from the manufacturer to
4 the back door of retail and non-retail pharmacies.
5 Retail pharmacies include chain, independent and
6 mass merchandisers, and non-retail pharmacies
7 include hospitals, clinics and other healthcare
8 channels.

9 Throughout this presentation, I also want
10 to introduce some of the measures which were used
11 during the analysis, some of them which might be
12 unfamiliar to you. Eaches are the number of
13 packets, bottles and vials of products shipped in
14 a unit. From this, we also use doses which are
15 calculated from extended units which were
16 calculated as one tablet equals one dose, 5
17 milliliters equals one dose, and 1 milliliter of
18 concentrated drop equals one dose.

19 And, finally, we used total dollars as a
20 measure to measure the amount of money that
21 pharmacies, hospitals and other healthcare
22 channels spent on acquiring an acetaminophen

1 product from manufacturers and wholesalers.

2 Here you see, between years 2004 and
3 2008, there was a 28 percent increase in the
4 overall acetaminophen market. Over 370 million
5 bottles and packets, or 24.6 billion doses, were
6 sold in year 2008. This translates to
7 approximately \$2.6 billion in sales.

8 Nearly 80 percent of the entire market is
9 over-the-counter products, or \$1.15 billion, and
10 this breaks down to about 50 percent of
11 over-the-counter combination products and 30
12 percent over-the-counter single-ingredient
13 products.

14 The remaining 20 percent were
15 prescription combination over-the-counter --
16 prescription combination acetaminophen products
17 which amounted to approximately \$1.4 billion in
18 sales.

19 This table shows the number of bottles
20 and packets, or Eaches, of over-the-counter
21 acetaminophen and prescription products sold from
22 the manufacturer to retail and non-retail channels

1 of distribution from years 2004 and 2008. And
2 basically it's reiterating some of the points that
3 were made in a previous graph. The last column
4 there shows the percent change between years 2004
5 and 2008.

6 This graph shows the same data from the
7 previous table except in a bar graph format, and
8 shows the proportion of over-the-counter
9 combination, which is on the bottom, and
10 over-the-counter single-ingredient, which is in
11 the middle, and the prescription combination
12 acetaminophen, which is on the top.

13 Again, this shows the total sales dollars
14 for acetaminophen products, the green bar
15 representing the entire market, and the purple
16 line representing the prescription acetaminophen
17 market, and the blue line representing the
18 over-the-counter acetaminophen market.

19 Now I will move on to a more detailed
20 analysis of the over-the-counter acetaminophen
21 products, beginning with combination acetaminophen
22 products. Nearly 60 percent of over-the-counter

1 products are combination products. There was a 36
2 percent increase in sales between year 2004 and
3 2008. Oral solid formulations accounted for
4 nearly three-quarters of sales in year 2008, and
5 oral liquid formulations accounted for about a
6 quarter of sales.

7 Now, in order to gain a perspective of
8 these products in children, we did a further
9 analysis of the oral liquid formulations at the
10 concentrated oral drop formulation to get a rough
11 estimate of use in children under the age of two
12 years. Since we are not able to obtain patient
13 demographic information from over-the-counter
14 product sales, we use this as a surrogate for use
15 in children under the age of two.

16 So the combination oral concentrated
17 drops dropped from 12 percent of oral liquid sales
18 in year 2004 to zero percent in year 2008, due to
19 the voluntary withdrawal of children's combination
20 oral drops by the manufacturer in year 2008.

21 Again, this graph illustrates the points
22 that were made in a previous graph. What we're

1 looking at here, the blue line represents the sale
2 of oral solid products for the combination
3 over-the-counter acetaminophen, and the pink line
4 here represents the oral liquid formulation for
5 the combination acetaminophen products.

6 Moving on, I will now be talking about
7 the single-ingredient acetaminophen products. The
8 single-ingredient over-the-counter products make
9 up approximately 40 percent of sales volume.
10 There was an 18 percent increase between year 2004
11 and 2008, and approximately 63 percent of these
12 products were oral solid formulations in year
13 2008.

14 Oral liquid formulations accounted for
15 approximately 27 percent of product sales, and of
16 that, the proportion of concentrated oral drops
17 was actually about 36 percent of all oral liquid
18 sales. The remaining 9 percent were oral solid
19 long-acting formulations which accounted for 9
20 percent of product sales in year 2008.

21 Again, this is a graph of the
22 single-ingredient -- only the single-ingredient

1 oral liquid formulations, and the blue bar here
2 represents all oral liquid formulations, and the
3 red line on the top represents the oral
4 concentrated drops for the single ingredients, and
5 you can see it's the most widely sold dosage form
6 for the single-ingredient liquid formulations.

7 We also examined the sale of
8 over-the-counter products by the strength of the
9 acetaminophen component. For the over-the-counter
10 combination products, the most common strength of
11 acetaminophen was 325 milligrams, followed by the
12 500 milligrams.

13 For the single-ingredient
14 over-the-counter products, 500 milligrams was the
15 most common acetaminophen dosage strength.

16 We also analyzed the most common
17 indications associated with the use of
18 acetaminophen products based on a survey of
19 office-based physicians across the country. The
20 SDI, Physician Drug and Diagnosis Audit is a
21 survey of approximately 3100 office-based
22 physicians that monitors the disease states and

1 physician intended prescribing habits. In this
2 survey, some over-the-counter drug products are
3 captured if it is mentioned during an office
4 visit.

5 So from here what we did was, for year
6 2008, we combined ICD-9 codes into larger
7 categories to get a diagnosis associated with use
8 for just the single-ingredient acetaminophen
9 products.

10 For ICD-9 -- moving from the bottom up,
11 from ICD-9s 150 to 239 were combined under
12 neoplasms. ICD-9 codes 460 to 466 were grouped
13 under acute respiratory infections, which include
14 colds and sinusitis. ICD-9 codes 710 to 739 were
15 grouped under disease of musculoskeletal system
16 and connective tissue, which include arthritic
17 conditions such as osteoarthritis and rheumatoid
18 arthritis. ICD-9 codes 780- to 789 were grouped
19 under fever and general symptoms. And ICD-9 codes
20 800 to 999 were grouped under fractures, sprains
21 and other injuries.

22 The rest were grouped under "all others,"

1 which basically included anything under the sun.
2 These range from migraines to hypertension to
3 asthma.

4 So for year 2008, the two largest
5 categories we found were acute respiratory
6 infections and other -- acute respiratory
7 infections and fractures and sprains and injuries.

8 Now I will move on into the prescription
9 combination acetaminophen products. I just want
10 to reiterate that all prescription acetaminophen
11 products are combination products.

12 In this analysis we used the SDI, Vector
13 One National to obtain prescription dispensing
14 data. SCI, Vector One is a national-level
15 projected prescription and patient tracking
16 service. It receives approximately 2 billion
17 prescription claims per year, and represents about
18 160 million unique patients. The number of
19 dispenses prescriptions are obtained from a sample
20 of approximately 59,000 pharmacies, which include
21 approximately -- nearly all retail pharmacies, and
22 represents nearly half of all retail prescriptions

1 dispenses nationwide.

2 The retail pharmacies in the sample
3 include national retail chains, mass
4 merchandisers, pharmacy benefit managers and their
5 data systems and provider groups.

6 So for the prescription acetaminophen
7 market, in year 2008 there were nearly 200 million
8 prescriptions dispensed for prescription
9 acetaminophen-containing products.

10 Hydrocodone/acetaminophen combination was by far
11 the largest -- most commonly dispenses
12 acetaminophen products, with approximately 123
13 million prescriptions, or 62 percent of the
14 combination acetaminophen prescription market.

15 Next was oxycodone/acetaminophen products with 31
16 million prescriptions, or 15 percent of the
17 market, and then followed by
18 propoxyphene/acetaminophen products with 21
19 million prescriptions and 10 percent of the
20 market, and codeine/acetaminophen products with
21 13.5 million prescriptions and 7 percent of the
22 market.

1 Non-narcotic acetaminophen combination
2 products accounted for approximately 5 percent of
3 the market.

4 And here this graph shows the points I
5 just made on an earlier slide, with the purple bar
6 representing the entire prescription acetaminophen
7 market. And you can see the line at the top, the
8 pink line, which represents the
9 hydrocodone/acetaminophen combination products.

10 We also analyzed the most commonly
11 dispenses strength for acetaminophen products, and
12 for year 2008 approximately 16 percent of
13 dispensed prescriptions were for strengths greater
14 than 500 milligrams. 40 percent were -- had 500
15 milligrams of strength of acetaminophen. And
16 approximately 29 percent were for strengths less
17 than 325 milligrams of acetaminophen.

18 So before I conclude, I want to present
19 some of the limitations for this analysis. For
20 the over-the-counter sales trend, it is estimated
21 that approximately 50 percent of all
22 over-the-counter sales are captured by the IMS

1 Health, IMS National Sales Perspectives. These
2 products -- products that are sold to
3 establishments without a pharmacy are not
4 captured, so those would be convenience stores, so
5 they would not capture sales to those channels.

6 We're also using sales volume as a
7 surrogate for use, so we're therefore unable to
8 determine user demographics. We're unable to
9 determine the frequency or amount of
10 over-the-counter product use at the consumer
11 level. And we are unable to determine concurrent
12 product use with other ingredients in other
13 products.

14 And also drug uses, which was shown to
15 you with the indications graph, refers to the
16 mention of a drug in association with a diagnosis
17 during an office-based physician -- patient visit.
18 This term may be duplicated by the number of
19 diagnoses for which the drug is mentioned and does
20 not always represent that a drug was actually
21 administered or prescribed during the office
22 visit.

1 So, in conclusion, the sale of
2 prescription and over-the-counter acetaminophen
3 products are growing, both in terms of units sold
4 and dollars. The most commonly sold strength for
5 the combination over-the-counter acetaminophen
6 products is 325 milligrams. For the
7 single-ingredient over-the-counter products --
8 that is, the most commonly sold strength is 500
9 milligrams. And for the majority of dispenses
10 prescription combination acetaminophen products
11 are 500 milligrams or greater for the
12 acetaminophen strength.

13 And that concludes my presentation.

14 DR. NELSON: Thank you. The next speaker
15 is Dr. Laura James, a guest speaker from the
16 University of Arkansas for Medical Sciences where
17 she is a professor in the Department of Pediatrics
18 and section chief of clinical pharmacology and
19 toxicology. And she's going to discuss the
20 metabolism and toxicology of acetaminophen.

21 DR. JAMES: Thank you. I'd like to thank
22 the organizers of this meeting for giving me the

1 opportunity to speak with you today, and I'm going
2 to share with you information about the role of
3 metabolism in acetaminophen toxicity.

4 I want to begin by first acknowledging
5 the generous support that I have received from the
6 NIH for studies on acetaminophen toxicity,
7 including a small business award granted to my
8 research lab to establish a diagnostic test for
9 acetaminophen toxicity.

10 The role of metabolism in acetaminophen
11 toxicity was established over 35 years ago. Liver
12 injury from acetaminophen was initially reported
13 following the ingestion of two large doses of
14 acetaminophen in two patients during suicide
15 attempts in 1966. In that same year,
16 investigators at the NIH established a murine
17 model of acetaminophen toxicity. They showed that
18 the drug was a dose-dependent hepatotoxin and also
19 that, at very high doses of the drug,
20 acetaminophen was converted to a reactive
21 metabolite that covalently bound to cysteine
22 groups on protein.

1 In addition, they showed that the degree
2 of covalent binding correlated with the severity
3 of the toxicity. This reactive metabolite was
4 identified to be N-acetyl-p-quinone imine --
5 excuse me, N-acetyl-para-quinone -- abbreviated as
6 NAPQI, as you can see why that abbreviation is
7 used. This reactive metabolite was shown to be
8 formed by the direct oxidation of the parent drug,
9 acetaminophen.

10 In subsequent years, the P-450 isoforms
11 involved in the metabolism of acetaminophen were
12 identified, and CYP2E1 is generally recognized to
13 be the one that is the most important from a
14 clinical standpoint, but other isoforms
15 participate in the metabolism of acetaminophen,
16 including CYP1A2, 3A4 and 2D6.

17 NAPQI reacts with glutathione through a
18 conjugation reaction to form 3-glutathione
19 acetaminophen.

20 In addition, it was found that
21 administration of cysteine to mice prevented the
22 development of toxicity. And this finding paved

1 the way for the modern-day development of -- for
2 the development of N-acetylcysteine which is the
3 modern-day treatment for acetaminophen toxicity.

4 This slide shows an overview of the
5 metabolism of acetaminophen. The drug primarily
6 undergoes metabolism through conjugation
7 reactions -- and the pointer is not working. A
8 minor metabolite of the drug formed by the
9 Cytochrome P-450 system is NAPQI, and normally
10 this metabolite, reactive metabolite is detoxified
11 through a conjugation reaction with glutathione.

12 With large doses of acetaminophen, the
13 metabolism of the drug is shifted away from
14 conjugation towards oxidation, and there is
15 increased formation of this reactive metabolite
16 NAPQI, glutathione is depleted, and the end result
17 is that there is the formulation of acetaminophen
18 protein adducts.

19 Numerous investigators have examined the
20 relationship between acetaminophen toxicity and
21 adduct formation, and these are data from Roberts,
22 et al., published over 20 years ago, in which

1 immunological approaches were used to characterize
2 the relationship between toxicity and covalent
3 binding.

4 As early as one hour in the mice, there
5 is a large amount of immunohistochemical staining
6 for acetaminophen protein adducts, and the
7 localization of this staining is in the central
8 lobular regions of the liver. I want to point out
9 that these are the same areas of the liver that
10 subsequently necrose, and you can see that, by six
11 hours in the mouse liver, the cells are beginning
12 to lyse, and there is vacuolization of cells and
13 loss of normal cellular integrity.

14 The time course of acetaminophen toxicity
15 in the mouse model is highly compressed compared
16 to what is observed in humans. These data show
17 both liver and serum time course data in a mouse
18 treated with acetaminophen. Adducts are formed in
19 the liver and peak at two hours, and then,
20 subsequently, adduct levels may be detected in
21 serum, and these time course data led to the
22 conclusion that the serum adducts are generally

1 thought to be a fall-out from liver-produced
2 adducts -- or the serum adducts are thought to be
3 derived in the liver.

4 Additional generated in the mouse model
5 show that adduct formation was dose-dependent. In
6 addition, the appearance of adducts in liver
7 preceded the elevation of hepatic transaminase
8 values in serum, and finally that treatment of
9 mice with the antidote, N-acetylcysteine, or NAC,
10 reduced both toxicity and hepatic protein adduct
11 formation.

12 A number of other mechanisms have been
13 examined as potential factors important the
14 mediation of toxicity. These other mechanisms
15 include oxidative stress, inflammatory responses
16 and mitochondrial injury and mitochondrial
17 permeability transition. These events are all
18 believed to occur downstream of metabolism.

19 A major goal of my research laboratory is
20 to take these data concerning metabolism and
21 adduct formation in the mouse model of
22 acetaminophen toxicity and to attempt to move this

1 into the clinical arena.

2 Early attempts to measure adduct levels
3 in patient serum were limited by complexity of
4 existing assays and also by the sensitivity of
5 these assays. In 1990, Dr. Hinson, et al.,
6 reported to use of an ELISA assay to measure
7 adducts in human serum. In this group of
8 patients, there were 11 patients that were
9 adjudged to be at risk for toxicity by the Rumack
10 nomogram. Five of these 11 received early
11 treatment with NAC within eight hours of the
12 overdose. These patients were protected from
13 toxicity and no adducts were formed or detected in
14 serum.

15 In contrast, six of the 11 patients
16 received treatment with NAC after eight hours, so
17 they had a delay in the onset of treatment. They
18 developed significant toxicity, and adducts were
19 detected in serum.

20 In a similar study, my laboratory
21 attempted to examine the issue of adduct formation
22 in adolescents and children with acute

1 acetaminophen overdose. We used Western Blot
2 assays and measured adducts in 51 children in this
3 study. For this group, there were six patients
4 who had severe overdose, which we defined as an
5 ALT value of greater than 1,000. In only one of
6 the six, and one for the total study, had adducts
7 detected in serum.

8 In 2002, we reported the development of a
9 new assay which was highly sensitive compared to
10 these previously reported assays. In this assay,
11 we use a serum sample, and the sample is treated
12 with either gel filtration or dialysis to remove
13 small molecules, such as the parent drug, or
14 acetaminophen metabolites. The samples are then
15 treated with protease digestion to remove
16 peptides, including acetaminophen cysteine, if it
17 is present in the sample. The resulting sample is
18 then injected onto the HPLC-EC machine where it is
19 analyzed for the presence of acetaminophen
20 cysteine adducts. And the quantitation of the
21 adducts is determined relative to an authentic
22 standard curve of acetaminophen cysteine.

1 Using this assay, we began, in a
2 collaboration with the acute liver failure study
3 group, which you will hear more about later
4 today -- we used this assay in collaboration with
5 this group to ask questions about the specificity
6 of the assay. And the opportunity that the acute
7 liver failure study group collaboration afforded
8 us was access to samples from patients with a
9 number of causes of acute liver failure.

10 In this collaboration, we assayed samples
11 from three patient groups. The first group was
12 patients with known acetaminophen-related acute
13 liver failure. The second group was patients --
14 or samples from patients with known cases of other
15 etiology of liver failure. These would be
16 patients with viral hepatitis or autoimmune
17 disease or Wilson's disease, et cetera. And,
18 finally, we assayed samples from patients with
19 acute liver failure of indeterminate etiology.

20 We also added samples from patients with
21 acute overdose who received early treatment with
22 NAC and were protected from the development of

1 toxicity. And, finally, I want to point out that
2 the analysis of these samples was conducted in a
3 blinded fashion. The laboratory personnel were
4 not aware of the diagnoses of these patients.

5 This slides provides an overview of the
6 results of that study. And these are adduct
7 values presented on the Y axis and different
8 sample groups across the X axis. And as noted by
9 the slide, patients with known
10 acetaminophen-related acute liver failure had
11 adducts in samples, and these are the median and
12 range of values of adducts in their patient
13 samples.

14 The second group represented patients
15 from known other causes of acute liver failure,
16 and no adducts were detected in this patient
17 group.

18 The third group represented patients that
19 were acute overdose patients that received early
20 treatment with NAC and had either low -- no to
21 very low levels of adducts detected in serum.

22 And, finally, the last two groups

1 represent patients from the acute liver failure of
2 indeterminate etiology group, and as you can see,
3 there were some patients who had adducts and there
4 were groups who did not have adducts detected in
5 serum. And the values of adducts were very
6 comparable to those values that we observed in
7 patients with acetaminophen-related liver failure.

8 In addition, the biochemical signature in
9 terms of the ALT, AST and bilirubin values for the
10 group that were adduct positive in the
11 indeterminate group were very similar to the
12 biochemical profile noted for patients with acute
13 liver failure related to acetaminophen.

14 There were 36 samples from the
15 indeterminate group, and again, these patients'
16 samples had undergone extensive testing for other
17 causes of acute liver failure, and the diagnosis
18 remained indeterminate.

19 Seven of 36 samples were found to be
20 positive for acetaminophen protein adducts for a
21 total of 19.4 percent. And in a similar
22 collaboration with the pediatric acute liver

1 failure study group, we found that 12 percent of
2 samples from patients with acute liver failure of
3 indeterminate etiology were positive for
4 acetaminophen protein adducts.

5 Over the next several years, through
6 grant funding from the NIH, we did a number of
7 studies to improve the efficiency of the
8 acetaminophen protein adduct assay, and to enhance
9 its sensitivity. And the next three studies that
10 I'm going to describe all were conducted using the
11 enhanced sensitivity version of the assay.

12 These data were published in electronic
13 format in May by Drug Metabolism and Disposition,
14 and will be available in paper copy in August of
15 this year.

16 In this study, we examined the
17 pharmacokinetics and clinical correlations of 53
18 adults with acetaminophen-induced acute liver
19 failure. And, again, this was through a
20 collaboration with the acute liver failure study
21 group.

22 These patients all had acute liver

1 failure as previously defined by this acute liver
2 failure study group. The diagnosis of
3 acetaminophen was made by a history of greater
4 than 4 grams per day acetaminophen use within
5 seven days of presentation, and detection of
6 acetaminophen on admission, or an ALT of greater
7 than 1,000 with a history of acetaminophen use
8 regardless of the acetaminophen level at
9 presentation.

10 We examined the relationship between
11 adduct levels and various clinical parameters
12 including lab values and outcomes. And the
13 correlation that was the highest was the
14 correlation for adducts and AST and for adducts
15 and ALT. And this slide shows the linear
16 correlation between adducts and AST values. The
17 lines are segregated according to the day after
18 overdose. And as depicted on the slide, this
19 analysis for samples obtained from day 3 after the
20 overdose, and day 4, had correlation coefficients
21 of .84.

22 In addition, we examined the

1 pharmacokinetics of adducts in these patients.

2 This was conducted in a subset of patients with an
3 N of 18, and these were patients for whom four or
4 greater samples were available for analysis.

5 And as demonstrated on the slide, many of
6 these patients still have detectable levels of
7 adducts as far as 10 to 11 days after the
8 acetaminophen overdose.

9 In a similar work, we reported the
10 pharmacokinetics of 157 children and adolescents
11 with acute overdose. This study was conducted in
12 collaboration with my colleagues in the PPRU.
13 Although this was a pediatric study and we did
14 have some children in the younger age group -- our
15 youngest patient was eight months of age -- the
16 majority of the subjects were adolescents and the
17 majority were female. 90 percent of these
18 patients were treated with the antidote
19 N-acetylcysteine.

20 This slide shows the range of adduct
21 values presented as a function of liver severity,
22 and you can see that the patients with the highest

1 liver injury also had the highest values of
2 adducts.

3 We also showed that early treatment with
4 NAC resulted in lower levels of adducts and that
5 if NAC treatment was delayed, the adduct levels
6 for those subgroups increased.

7 This data show the pharmacokinetic plots
8 for individual patients for whom we had greater
9 than two samples available for analysis. And
10 similar to the adult data that I just showed you,
11 adducts were detectable in some of these patients
12 as late as eight, nine and ten days after the
13 overdose.

14 In order to establish the sensitivity
15 and specificity of the assay, receiver operator
16 curve analysis was performed. Using a reference
17 value of ALT of greater than 1,000, we were able
18 to select a cut point of 1.1 for adduct values,
19 and this generated a sensitivity of 97 percent and
20 95 percent specificity for the assay.

21 Finally, I want to mention work that we
22 have done in collaboration with Dr. Paul Watkins

1 at the University of Chapel Hill. In this study,
2 we measured adducts in patients who were receiving
3 therapeutic doses of acetaminophen. In this
4 study, there were 52 healthy volunteers that were
5 housed as inpatients over a 14-day period.
6 Patients were randomized to either active
7 treatment with acetaminophen or to placebo, and
8 the treatment -- active treatment period was a
9 seven-day period.

10 Patients were stratified by change in ALT
11 from baseline. A responder was defined as a
12 patient who had a greater than two-fold elevation
13 in the ALT during treatment with acetaminophen
14 compared to the baseline ALT value.

15 Non-responders had a change in ALT that never was
16 greater than 1.5-fold elevation, and intermediate
17 responders fell between these two cut points.

18 This slide is an overview of the raw data
19 from that study. On the left are ALT values for
20 the population, and on the right are adduct values
21 for the population. The black line represents
22 placebo-treated patients, and as you can see on

1 the ALT graph, the ALT values remained constant in
2 those patients that were treated with placebo, and
3 there were no adducts detected in the placebo arm
4 of that study either.

5 The green line reflects the active period
6 with acetaminophen -- or the period of active
7 treatment with acetaminophen.

8 The responders, by definition, had a
9 greater than two-fold change in ALT from baseline
10 values, and as demonstrated on the right,
11 responders also had formation of adducts that was
12 very similar to the curve that we noted for the
13 intermediate responder group.

14 What is noteworthy is that all patients
15 that received acetaminophen had detection of
16 adducts. When the responder and the intermediate
17 responder group were combined, these AUC profiles
18 were significantly greater than the AUC profile
19 for the non-responder group.

20 Now, it's important to put these data
21 into perspective. The data from the therapeutic
22 dose group -- the maximum value of adducts for

1 this group are reported -- or shown on the slide
2 with the red line. So the peak adduct levels in
3 this population were .3. In contrast, adduct
4 values from patients with acute liver failure from
5 acetaminophen overdose were two orders of
6 magnitude higher than those values noted upon
7 therapeutic exposure.

8 Lastly, I want to touch on the issue of
9 patient susceptibility, and this is an issue that
10 is mentioned throughout the literature and is of
11 interest to a number of people, and there are a
12 number of researchers who are beginning to look
13 into this issue.

14 At this point in time, we really do not
15 have a lot of good data to suggest that there may
16 be patient susceptibility, but in this day of
17 pharmacogenetics and pharmacogenomics, I think
18 it's very reasonable to postulate that, in the
19 future, we may be able to identify subsets of
20 patients who, because of their pharmacogenetics,
21 may have a predisposition toward acetaminophen
22 toxicity. And this is ongoing work in a number of

1 pharmacogenetic labs across the country.

2 In preparation for this talk, I noticed
3 that one investigator, Dr. Michael Court at Tufts
4 University, currently has a trial registered on
5 clinicaltrials.gov in which he is examining
6 polymorphisms for glucuronidation, sulfation and
7 for 2E1 metabolism. And this data may give us
8 additional insight into whether or not there is
9 significant patient susceptibility with respect to
10 acetaminophen use.

11 Lastly, I want to just touch on the issue
12 of drug/disease interaction, and the best
13 interaction that has been recognized in the
14 literature is that for alcoholism and
15 acetaminophen use, but there are many other
16 drug/disease implications that need to be studied,
17 and hopefully in coming years we will have more
18 information on that.

19 I want to conclude and summarize by
20 stating that the toxicity of acetaminophen is
21 largely influenced by metabolism of the drug.
22 Acetaminophen protein adducts reflect metabolism

1 of the drug and are a specific biomarker of
2 acetaminophen toxicity in patients.

3 However, the clinical significance of
4 lower levels of adducts in adults receiving 4
5 grams per day is unclear. And in my own research
6 laboratory, we were -- we are moving forward with
7 this issue, and we are about to embark on
8 proteomic studies in which we will identify
9 proteins that are adducted by acetaminophen and
10 look at these proteins in various populations of
11 patients, including patients receiving therapeutic
12 exposure and patients with overdose.

13 And, finally, continued study of patient
14 susceptibility is needed and hopefully, in our
15 modern-day era of pharmacogenetics and genomics,
16 we will have additional forthcoming information
17 about the contribution of genetic variability to
18 acetaminophen metabolism.

19 And then I want to close by acknowledging
20 the grant support of NIH and also to mention my
21 numerous collaborators. Thank you.

22 DR. NELSON: Thank you. We do have a few

1 minutes to ask some questions of the speakers from
2 the FDA, so if anybody would like to ask a
3 question, please raise your hand and we'll
4 identify you.

5 DR. FARBER: This is for Arlene Solbeck.
6 In regards to the labeling of combination
7 products, besides the individual substances that
8 are included in the labeling, are the indications
9 also required for each of those products?

10 MS. SOLBECK: The answer is yes.

11 DR. NELSON: Are there any other
12 questions for the FDA speakers?

13 DR. OMOGUI: This question is for
14 Dr. James. Are there any studies that show
15 toxicity at lower levels -- at lower dosing levels
16 of acetaminophen over prolonged periods of time?
17 Because the number of 4 grams a day is seen widely
18 in the literature, but in the study you presented,
19 you're already getting protein adducts after just
20 seven days on a dose of 4 grams a day. So in the
21 case of prolonged exposure of months, does the
22 toxicity occur at lower dosing levels, and what

1 studies are out there about that?

2 DR. JAMES: Most of the studies are
3 relatively short-term studies, in the interval of
4 five to seven days, and I'm not aware of any
5 long-term studies.

6 DR. NELSON: Could you do me one favor
7 and turn your placards a little bit towards me. I
8 just don't see them very well, so it's hard to
9 know who -- okay. Dr. Stergachis is next.

10 DR. STERGACHIS: Thank you. Also for
11 Ms. Solbeck. The duration of time between
12 proposed and final rulemaking, it looks like it's
13 going in the right direction from over ten years
14 for the original monograph to somewhere between
15 one to three years on the liver injury. Could you
16 comment on what are some attributes or some
17 contributors to shortening the amount of time
18 between proposed rulemaking and final rulemaking?

19 MS. SOLBECK: Well, of course, whenever
20 we get the assignment to go ahead and work on the
21 progressing rule, there's always other actions
22 that are going on around and there are always

1 priorities that take us away, partially, from some
2 of the things that we're doing, but lately what
3 we've done, I think, is that we have established a
4 team -- teams of people who are the ones that are
5 going to focus primarily on these particular
6 actions that we have to get done. And then we do
7 run timelines and we do a lot of work in terms of
8 how long it's going to take us to get it done, and
9 we do everything we can in order to push the time
10 and try and get it as quick as possible.

11 And I think we have been succeeding in
12 the latest few rulemakings that we've been able to
13 publish.

14 DR. NELSON: Dr. Kweder?

15 DR. GANLEY: Can I just add something to
16 that? Could I -- this is Charlie Ganley. Are you
17 talking about the time from the 1988 rule? I
18 think one of the difficulties is when we finalize
19 a monograph, you're stating that it's generally
20 recognized as safe and effective.

21 If you have a pending safety issue, how
22 do you make that finding? And so, as you can see,

1 it's been done sort of piecemeal, trying to
2 address this issue, but it's very difficult to
3 come to some conclusion on a monograph, saying
4 that it's generally recognized safe and effective
5 when you still have this pending issue regarding
6 liver injury. Because then it becomes much more
7 difficult, if we make that finding, to go back and
8 try to correct it after we've come to a final
9 rule.

10 DR. KWEDER: This is Sandra Kweder. I'll
11 add to that. When we -- the whole process of
12 rulemaking is -- it sounds a bit pointy-headed,
13 but when we put forward proposed rules and final
14 rules, we are in the -- there are -- proposed and
15 final rules sort of take their place in the queue
16 of multiple proposed or final rules that the
17 agency, the department and the government has
18 before them.

19 And once they leave our hands in the
20 center, they go multiple other places. And so a
21 lot of the lead time, the scientific time, is
22 under our control. But once it leaves us, it is

1 not very much under our control at all.

2 DR. NELSON: Dr. Kramer?

3 DR. KRAMER: Judith Kramer. I have a
4 question for Dr. James. Could you clarify -- in
5 your slides, the study by Dr. Paul Watkins in
6 healthy volunteers with approved doses was listed
7 as being presented. Has that been published?

8 DR. JAMES: No. That was presented in
9 abstract formation.

10 DR. KRAMER: In 2007?

11 DR. JAMES: Yes.

12 DR. KRAMER: I think that would be
13 important to get in the literature.

14 DR. JAMES: We are working on that.

15 Thank you.

16 DR. NELSON: Dr. Chojkier?

17 DR. CHOJKIER: The paper by Dr. Watkins,
18 he had the study published a few years ago, I
19 think in 2006, where 4 grams of acetaminophen in
20 different groups with and without narcotics
21 combination, prescription medication, inducing in
22 a third of the patients elevation greater than

1 three-fold upper limit of normal.

2 DR. KRAMER: The study showing the
3 parallel adduct measurement has not been
4 published?

5 DR. CHOJKIER: Correct.

6 DR. NELSON: Dr. Vaida?

7 DR. VAIDA: Yes. For Arlene, I had a
8 question on that labeling also, but not the
9 indication. Is it -- the combination products, do
10 they need the dosage strength on the front? It
11 looks like the single does.

12 MS. SOLBECK: The single does. I don't
13 think the dosage -- the combination dosage does.

14 DR. CHANG: Yes. Okay. A lot of the
15 time when we do labeling, if the ingredient is in
16 the official monograph, then the name of the
17 product -- the name of the active ingredient and
18 also the pharmacological category of the drug
19 needs to be on the PDP. And also we always try to
20 encourage to include the dosage for each
21 ingredient to be on the PDP.

22 Then, at the back of the Drug Facts

1 labeling, under the active ingredient, each
2 ingredient will be listed alphabetically. So if
3 we have three combinations, then acetaminophen
4 will be the first one listed, and then the dose
5 will also be listed on the active ingredient for
6 each ingredient.

7 MS. FERGUSON: Could you please state
8 your name for the record.

9 DR. CHANG: Yes. My name is Marina
10 Chang, and I work with the Division of Regulatory
11 Development in the Office of Nonprescription
12 Products.

13 MS. FERGUSON: And if everyone could
14 remember to state their name first, before they
15 speak. Thank you.

16 DR. NELSON: Did that answer your
17 question, Dr. Vaida?

18 DR. VAIDA: I'm taking that it does. I'm
19 looking at that slide 16, and I'm -- was the
20 answer that the strength is on there with the
21 combination products?

22 DR. CHANG: On slide 16, no. She was

1 just doing a mock-up, so the strength was not on
2 the --

3 DR. VAIDA: But the strength will be on
4 there?

5 DR. CHANG: Yeah, the strength will be on
6 there.

7 DR. VAIDA: Okay.

8 DR. NELSON: Dr. Krenzelok?

9 DR. KRENZELOK: Thank you. Krenzelok.

10 This question is for Dr. James. In our briefing
11 materials, there was a lot of information about
12 pediatric liquid formulations, and Dr. James
13 discussed metabolism, but my perspective on her
14 discussion of metabolism dealt primarily with
15 adult patients. And then, toward the end, she
16 talked about vulnerable and susceptible
17 populations. I'm just wondering if she could
18 share for us some information on metabolism of
19 acetaminophen in the pediatric population,
20 especially maybe kids less than ten years of age,
21 and what implications that may have in terms of
22 toxicity regarding metabolism.

1 DR. JAMES: Yes. In general, and this is
2 based on some older studies of metabolism in
3 acetaminophen in children, and in general it is
4 believed that the glucuronidation and sulfation
5 pathways may have greater capacity than that noted
6 in adult patients, but there's also not a lot of
7 information about very young children. There's
8 actually one study that is under review now where
9 they want to look at metabolism of the drug in
10 very long, such as pre-term and newborns, where
11 it's used commonly in neonatal intensive care
12 units.

13 But I think your main question was with
14 respect to metabolism in the older child, and in
15 general it's assumed that perhaps the sulfation
16 and glucuronidation pathways may be at greater
17 than adult levels, and that there may be relative
18 protection in children compared to adults.

19 Also, just in general, in the pediatric
20 toxicology literature, as you know, there are
21 fewer children, compared to adults, that present
22 with acute overdoses, and some of that may be

1 related to time to presentation to the hospital.
2 Adults tend to get to hospitals later in the onset
3 of an overdose than a pediatric patient and the
4 family would.

5 DR. NELSON: I think for this section
6 will take one final questions from Dr. Benowitz,
7 and then we'll ask if we could hold the rest of
8 the questions till the later question-and-answer
9 session.

10 DR. BENOWITZ: Two brief questions for
11 Dr. James. One, when you talk about drug
12 interactions, there are a lot of drugs that are
13 inducers of CYP2E1, and do we know anything about
14 those being risk factors for liver damage?

15 And the second question is, is there any
16 evidence or biological plausibility that opiates
17 per se could enhance the toxicity of
18 acetaminophen?

19 DR. JAMES: Could inhibit or --

20 DR. BENOWITZ: No. Could opiates per se
21 enhance the toxicity?

22 DR. JAMES: I believe that the data that

1 Paul Watkins published in the JAMA paper in 2006
2 in which they looked at acetaminophen/opioid
3 combinations and compared to acetaminophen only --
4 and in those studies, the opioid did not
5 contribute to -- was not found to be a
6 contributory factor to the ALT elevation.

7 So the patients that had the ALT
8 elevations that received the combination products
9 had the same ALT elevations as the patients that
10 received the single-ingredient acetaminophen.

11 I think the first part of your question
12 was clinical significance of P-450 inducers in
13 other drugs. You know, there are -- my review on
14 this is that there are case reports from the older
15 literature reporting that. I don't know that we
16 have really good controlled data looking at,
17 particularly, 2E1 inducers in the setting of
18 acetaminophen, of course, you know, other than the
19 data that we have about alcoholism.

20 DR. NELSON: Before we do move on, there
21 was one just clarification from Dr. Kramer for
22 Dr. Chang.

1 DR. KRAMER: Judith Kramer. I just have
2 a question for Dr. Chang to clarify the answer
3 that you gave concerning the required PDP labeling
4 for combination products. When you first
5 answered, you said that you required the name and
6 the indication, but encouraged manufacturers to
7 put the dose. And then, at the end, you said it
8 will be there. Could you clarify whether the dose
9 strength will be required in each ingredient.

10 DR. CHANG: Yes. I'm sorry. I was just
11 coming into this. The dose strength for the
12 monograph is not required to be on the PDP. But
13 at the back of the Drug Facts labeling, under the
14 active ingredient, the dose will be there.

15 DR. KRAMER: So you have to go to two
16 places? You cannot see it on the PDP?

17 DR. CHANG: Yes.

18 DR. KRAMER: Thank you.

19 DR. NELSON: Okay. I'd like to next ask
20 Linda Suydam from the Consumer Healthcare Products
21 Association to come up and speak.

22 DR. SUYDAM: Good morning, and thank you

1 for holding this important meeting to discuss
2 interventions to help reduce liver injury from
3 acetaminophen overdose. I'm Linda Suydam, and I'm
4 president of the Consumer Healthcare Products
5 Association, and I'm here today representing the
6 CHPA Acetaminophen Task Group, which you see on
7 this slide.

8 These companies manufacture more than 90
9 percent of over-the-counter, or OTC, acetaminophen
10 medicines in the United States, including both
11 brand and store brand products. This represents
12 about half of the acetaminophen taken in this
13 country, with the other half being prescription
14 acetaminophen medicines.

15 First and foremost, let me say that we
16 share the same goals as the FDA and the members of
17 this committee: To encourage the safe and
18 appropriate use of all acetaminophen-containing
19 medicines. We recognize that the risk from
20 acetaminophen overdose is a serious public health
21 concern, and we agree with the FDA that, together,
22 we can take steps to minimize this problem.

1 In our presentation today, I will provide
2 an overview of the epidemiology of acetaminophen
3 use with a specific focus on the benefits of
4 over-the-counter combination products, update you
5 on what the industry has done since 2002, and
6 provide you with the task group's recommendations.

7 Dr. James Lewis from Georgetown
8 University Medical Center will share his analysis
9 of safety data on OTC combination products.
10 Dr. Lewis is the director of hepatology at
11 Georgetown University Hospital and professor of
12 medicine at Georgetown University School of
13 Medicine. He is also an expert in drug-induced
14 liver injury and acute liver failure, and a member
15 of the liver transplant team. Then I will come
16 back to detail the industry-wide research and
17 education initiative that CHPA is proposing, and
18 our commitment to carry it out.

19 But before we discuss the program to
20 address this concern, we need to understand the
21 problem we're trying to solve. The epidemiology
22 of liver toxicity is complicated. There are very

1 distinct categories of acetaminophen products and
2 very distinct categories of misuse. These include
3 OTC single ingredient, OTC combination products
4 and prescription combination medicines. And
5 within these categories, there's unintentional and
6 intentional misuse.

7 Today, as representatives of the
8 over-the-counter industry, we will be focusing on
9 OTC combination medicines, and more specifically,
10 the unintentional use of these medicines. Later,
11 in a separate presentation, McNeil, the maker of
12 Tylenol, will discuss single-ingredient
13 acetaminophen products.

14 As I mentioned, OTC medicines represent
15 about half -- 52 percent -- of all acetaminophen
16 products. What is not widely recognized is that
17 the prescription products represent nearly half of
18 the overall acetaminophen use in the United
19 States.

20 Of all acetaminophen use, McNeil
21 represents about 27 percent, with Tylenol as its
22 main brand. Most of the remaining 25 percent of

1 OTC products are store brand acetaminophen and
2 combination products containing acetaminophen.

3 So with this as background, let me review
4 CHPA's position on the issue before us. The task
5 group strongly supports the continued availability
6 of combination medicines containing acetaminophen
7 because, as FDA stated in its briefing book, OTC
8 combination products are rarely associated with
9 serious liver injuries.

10 We strongly disagree with the FDA's
11 statement that these products are only available
12 for convenience. The data show that OTC
13 combination products provide significant benefit
14 to consumers, including the risk of dosing errors.

15 We support FDA's recommendation that
16 pediatric liquid products be sold with appropriate
17 dosing devices and that the label include dosing
18 information for children under the age of two. We
19 support continued availability of 1,000-milligram
20 single dose and 4,000 milligram maximum daily
21 dose. And finally, and most importantly, we
22 support a broad-based research and education

1 program that includes both over-the-counter and
2 prescription medicines because, according to the
3 FDA analysis of a sample of the death cases
4 reported in the AERS database in 2005,
5 prescription products contribute about 60 percent
6 of acetaminophen-related deaths, with OTC products
7 contributing roughly 40 percent of the reported
8 cases.

9 Of all of those cases, 82 percent were
10 the result of intentional harm or people
11 attempting suicide, and very few -- 6 percent --
12 involved combination products.

13 Pointing out the part the prescription
14 acetaminophen has in these overdoses is in no way
15 meant to deflect from the role that OTC
16 acetaminophen products play in liver injury cases.
17 Rather, we want to accurately and appropriately
18 separate prescription and OTC data and to
19 differentiate the interventions that may be
20 appropriate to each.

21 So we urge the committee to keep these
22 data in mind when considering the options before

1 them today because it's only through addressing
2 the full scope of the problem that we will be able
3 to maximize our impact.

4 Before we present our proposed education
5 program, I'd like to take this opportunity to
6 update the committee on the steps industry has
7 taken since we last met in 2002.

8 At the time of that advisory committee
9 meeting, industry had already begun to voluntarily
10 enhance the labels on their
11 acetaminophen-containing products. These label
12 enhancements included increasing the awareness of
13 acetaminophen as an ingredient in combination
14 products by listing the ingredient and its
15 function in consumer-friendly terms on the
16 principal display panel or the front of the
17 package in all combination products, highlighting
18 the active ingredient, including acetaminophen, on
19 the Drug Facts label, adding an overdose liver
20 warning, and warning consumers against taking one
21 acetaminophen-containing product with another.

22 In fact, I'll pass around samples so that

1 you might see what is already on the market today
2 with both the principal display panel and the
3 acetaminophen label, as well as the active
4 ingredient and the warning statement on the back
5 of the box.

6 In 2006, FDA proposed even stronger
7 language, including making the liver warning more
8 explicit. At that time, many products already
9 carried this stronger language, and after that
10 announcement, most of our members moved ahead and
11 voluntarily strengthened the liver warning.

12 CHPA established an educational
13 foundation and website, OTCsafety.org, designed to
14 ensure the safe use of all over-the-counter
15 medicines. The foundation conducts public
16 awareness campaigns on the safe use of all OTC
17 medicines. CHPA is also an active participant in
18 an initiative led by the Centers for Disease
19 Control and Prevention to address accidental
20 ingestions of all OTC medicines by children. This
21 should lead to actions which will reduce
22 unsupervised overdoses of acetaminophen.

1 And now, in 2009, all manufacturers are
2 working to implement FDA's final rule on OTC
3 analgesic warnings which reflect many of the
4 points I just outlined.

5 While we believe that, cumulatively,
6 these efforts benefit consumers, we've also
7 learned some valuable lessons about how to make
8 them more meaningful and impactful, and we've
9 incorporated these lessons into the program we
10 will share with you today.

11 As I've already mentioned CHPA strongly
12 supports over-the-counter availability of
13 combination products. There are two types of
14 over-the-counter combination products containing
15 acetaminophen: Those that offer more effective
16 treatment of the same symptoms, such as pain in
17 migraine sufferers; and those whose benefits lie
18 in the concurrent treatment of multiple symptoms,
19 including pain and fever.

20 Let's look at data supporting these
21 benefits, starting with the first type,
22 combination analgesics. Headache provides an

1 excellent example of how people can get superior
2 pain management by combining OTC ingredients with
3 different modes of action. A recent multi-arm
4 study in headache demonstrates that combining
5 acetaminophen with other ingredients allows for
6 dose sparing of both acetaminophen and aspirin.

7 Here we see the proportion of people who
8 experienced a 50 percent increase in pain relief.
9 The combination of 500 milligrams of aspirin with
10 400 milligrams of acetaminophen plus caffeine, all
11 represented by the yellow line, provided
12 statistically significant pain relief over both
13 1,000 milligrams of acetaminophen as well as 1,000
14 milligrams of aspirin, represented by the red and
15 green lines.

16 Dr. Stephen Silberstein, director of the
17 Jefferson Headache Center in Philadelphia, and a
18 researcher in the field of headache, is here today
19 to answer your questions about this condition and
20 the use of combination products for its treatment.

21 Treatment of the common cold is the area
22 where the second type, the multi-symptom

1 combinations, are most frequently used, and it's
2 well-established that the common cold presents
3 with more than one symptom.

4 In this four-year prospective study,
5 researchers tracked the symptoms of 226 colds over
6 seven days. The data show that people experienced
7 the majority of these symptoms, including
8 headache, concurrently. Data also show that
9 people also seek concurrent treatment of their
10 symptoms, and combination products effectively
11 provide relief for these concurrent symptoms.

12 Because the ingredients in combination
13 products are matched in terms of their amount and
14 dosing interval, it would be difficult for
15 consumers to try to schedule and accurately dose
16 each of these medicines individually. In addition
17 to effectively treating symptoms of a cold,
18 combination products also simplify dosing.

19 We know from studies involving thousands
20 of people that fixed-dose prescription medicines
21 reduce dosing errors. The data show that people
22 taking these combinations were more likely to

1 follow proper dosing, had reduced pill burden and
2 costs, and improved outcomes compared to those who
3 used multiple mono-ingredient medicines. In fact,
4 a systematic review and meta-analysis of nine
5 trials involving 20,000 people showed that
6 fixed-dose prescription combination products
7 reduced the risk of non-compliance to dosing by 25
8 percent versus single-drug medicines.

9 We think these findings are relevant to
10 this committee's deliberations regarding
11 increasing compliance to dosing directions.

12 Dr. Franz Messerli from Columbia
13 University who conducted that meta-analysis is
14 here today to answer your questions about reducing
15 dosing errors with combination products.

16 The positive benefit/risk profile of
17 combination products is further supported by the
18 low rate of serious adverse events from overdose
19 for acetaminophen-containing over-the-counter
20 combination products. Dr. Lewis will be up
21 shortly to review this safety data. But before I
22 turn the lectern over to him, I'd like to recap

1 the Acetaminophen Task Group's recommendations.

2 The task group strongly supports the
3 continued OTC availability of combination
4 medicines containing acetaminophen, given its rare
5 association with serious liver injuries and
6 benefits to consumers.

7 We support FDA's recommendations that
8 pediatric products be sold with appropriate dosing
9 devices, and that the label include dosing
10 information for children under the age of two.

11 CHPA supports continued availability of a
12 range of strengths and doses, as they provide
13 consumers with a range of doses to achieve
14 satisfactory pain relief.

15 And, finally, and most importantly, we
16 support a broad-based research and education
17 program that includes both OTC and Rx medicines
18 which I will outline shortly.

19 As I mentioned, we have Dr. Messerli and
20 Dr. Silberstein here to answer your questions. We
21 also have Dr. Saul Shiffman, a behavioral sciences
22 expert from the University of Pittsburgh, who can

1 discuss the characteristics of effective consumer
2 research and education programs.

3 I'd like now to turn to Dr. Lewis.

4 DR. LEWIS: Thank you, Dr. Suydam.

5 Members of the advisory committee, FDA
6 staff, ladies and gentlemen, good morning. My
7 specific task today, building on what you've just
8 heard, is to review the fatal events associated
9 with the over-the-counter combination products
10 containing acetaminophen.

11 Having myself been a member of several
12 FDA advisory committees and panels over the years,
13 I know how essential your deliberations are today
14 on any public health concern, such as the one that
15 we have before us.

16 As a practicing hepatologist at a large
17 university transplant center, while these cases
18 are rare, I certainly do see my share of severe
19 acetaminophen liver injury. And I'm probably not
20 different from most physicians who tend to lump
21 all acetaminophen-containing products into the
22 same category when we're confronted with acute

1 liver failure, certainly when it comes to the
2 patients who are referred in for our transplant
3 evaluation.

4 But as I'll demonstrate to you, the OTC
5 combination products, despite their widespread
6 use, are, in fact, the least likely acetaminophen
7 formulations to be associated with fatalities,
8 especially when they're compared to the
9 prescription combinations which, as you've already
10 heard, are all combinations and mostly contain an
11 opioid or a narcotic.

12 Specific to my remarks today, I've
13 analyzed the data contained in two large U.S.
14 databases dealing with the fatal acetaminophen
15 overdoses which includes both adults and children,
16 the Toxic Exposure Surveillance System, or TESS,
17 which is run by the American Association of Poison
18 Control Centers -- has been reviewed from 2005,
19 and that's contained in your briefing book by the
20 FDA. We've also looked at the latest TESS data
21 from 2007.

22 In addition, cases from the FDA's

1 spontaneous adverse reporting system, or AERS,
2 which you've already heard about, and contained in
3 the briefing document, will also be reviewed.

4 Both the TESS and the AERS databases show
5 very similar outcomes with respect to the
6 over-the-counter combination products. You can
7 see in red on the left, looking at the data from
8 TESS from both 2005 and 2007, reporting fatal
9 exposures with acetaminophen during those years,
10 only 11 percent and 10 percent from those two
11 years were related to the over-the-counter
12 combination products.

13 In contrast, nearly 50 percent of the
14 fatalities were associated with the
15 single-ingredient acetaminophen, and 40 percent
16 with the prescription combination narcotic
17 medications during those two years.

18 When we examine the AERS database, the
19 FDA selected a random sample of 100 cases from
20 accrued death cases associated with acetaminophen
21 from 2005. Of these 100, 72 cases remained for
22 analysis after duplicates and cases with missing

1 information were excluded.

2 In nearly half of these 72 cases, 35
3 individuals, or 49 percent, the actual cause of
4 death was not stated. The other half broke down
5 almost evenly, with 25 percent reporting hepatic
6 events and 26 percent reporting either a cardiac
7 or respiratory event as the cause of death.

8 In many of these cardiopulmonary deaths,
9 the narcotic component of the prescription
10 acetaminophen combination was thought to have
11 played a causative role.

12 Overall, the 2005 AERS data are very
13 similar to those seen with TESS in terms of the
14 low number of cases associated with the
15 over-the-counter combination products. You can
16 see here in red, of 81 acetaminophen products
17 mentioned with the 72 deaths, only 6 percent of
18 the products recorded were OTC combinations. In
19 contrast, 33 percent were related to the
20 single-ingredient acetaminophen, and the vast
21 majority, 59 percent, due to the prescription
22 combination drugs.

1 I also thought it would be important to
2 break down the cases into those taking
3 acetaminophen with suicide intent as opposed to
4 unintentional overdoses. This slide illustrates
5 that suicide was the major cause in all three
6 database samples.

7 In the TESS cases from 2005 and 2007,
8 suicides accounted for approximately 60 percent of
9 all cases. 20 percent of the cases were
10 unintentional overdoses. And in the remaining
11 about 20 percent, it was unknown whether the
12 overdose was a suicide or was unintentional.

13 Similar to the TESS findings, the
14 majority of the AERS cases in all three product
15 categories, more than 80 percent, were also
16 associated with suicide and intentional misuse.

17 Looking specifically at the cases
18 associated with the OTC combinations, you can see
19 that, in the TESS 2005 data, only a single case
20 was considered unintentional. Of the 23 cases
21 associated with the OTC combination in TESS 2007,
22 there were only three of 23 cases considered

1 unintentional. Of the five over-the-counter
2 combinations mentioned in the AERS database in
3 2005, again, only one was associated with an
4 unintentional overdose.

5 When we compare the number of deaths in
6 these databases to the number of patients using
7 various acetaminophen products, it's apparent that
8 the rate of these fatal events associated, again,
9 with the OTC combination products in particular is
10 low and disproportionately less in terms of
11 fatalities compared to the other formulations.

12 As we see in the IMS data on the right
13 side, chosen from 2005 so it corresponds with the
14 TESS and AERS databases that the FDA are using
15 from the same year, the OTC combination products
16 represented more than one-third of all
17 acetaminophen units sold, yet the percentage of
18 fatal events was much lower compared to the other
19 formulations. Again, you can see that is 11
20 percent and 6 percent.

21 So, in conclusion, the results of my
22 review of these TESS and AERS databases

1 demonstrate that the acetaminophen formulations
2 least likely to be associated with a fatal outcome
3 are, in fact, the OTC combination products,
4 especially when we compare them to the
5 prescription combinations including narcotics.

6 While acetaminophen overdoses can be
7 associated with acute liver failure, with death
8 and transplant, cases due to the OTC combination
9 products are infrequent and proportionately less
10 in terms of their overall use. Therefore, the
11 data do not support the need to remove
12 acetaminophen from OTC combination products.

13 Thank you for your attention, and I'll
14 have Dr. Suydam return to conclude with her
15 remarks.

16 DR. SUYDAM: Thank you, Dr. Lewis.

17 Over the next two days, we will hear
18 discussion about various options to address
19 acetaminophen overdose. We believe the most
20 effective intervention is education. But it must
21 be done right, based on science and evaluated
22 through research, and it cannot be done alone.

1 CHPA is committed to launching a new broad-based
2 education program on the appropriate use of
3 acetaminophen and the potential risk of liver
4 injury associated with overdose.

5 So what is new about our proposal and why
6 now?

7 First, up until now, CHPA's general
8 education focus on analgesics has been on label
9 awareness, adherence and safe use of medicines.
10 Our proposed initiative is the first
11 industry-wise, industry-supported education
12 program focused specifically on acetaminophen and
13 would include all members of our acetaminophen
14 products task group, and importantly include
15 healthcare partners involved in prescription
16 acetaminophen medicines.

17 Secondly, while much of our label
18 improvements have been done on a voluntary basis,
19 we now have a finalized rule from the FDA that
20 will make these changes universal.

21 Additionally, new information has been
22 made available to the CHPA through this advisory

1 committee process. This information highlights
2 the need for a robust education program that
3 includes more than one company, more than just the
4 FDA and more than just OTC medicines. The data
5 clearly tell us that this is both an OTC and
6 prescription issue.

7 So to ensure all professionals involved
8 in patient care are included, CHPA and the
9 American Pharmacists' Association have created a
10 consortium of key parties that will be actively
11 participating in this educational campaign. The
12 goal is to ensure that clear and consistent
13 messages are delivered to our targeted audiences
14 at teachable moments.

15 The consortium will meet in July to start
16 this initiative. I'll talk more about this
17 multiplying effect when I detail the various steps
18 of the program.

19 CHPA believes that research -- this
20 research and education program, which we have
21 already begun designing and conducting, will be
22 successful and distinct from past efforts. It

1 takes a step-wise approach that will be based on
2 research, comprehensive in its approach,
3 consistent in its message, targeted to specific
4 user populations, tested and validated.

5 Let me walk you through each step of the
6 research and education program.

7 First, we will use qualitative and
8 quantitative research to identify both cognitive
9 and behavioral factors contributing to potential
10 acetaminophen overdoses. For example, we know
11 that liver injury can be caused by taking too much
12 acetaminophen, but we do not know enough about why
13 and when this happens. We'll be fielding our
14 quantitative data in July, and we now have
15 insights from recently collected qualitative data.

16 Based on that data, one could hypothesize
17 that the target user population could include
18 heavy drinkers, including binge drinking, and
19 those who suffer from chronic pain. We will be
20 validating these assumptions with our quantitative
21 research.

22 Ultimately, our goal is to reduce the

1 number of people who do not follow the label
2 through -- either by exceeding the maximum daily
3 dose, exceeding the single dose, speeding up the
4 dosing interval, concomitant use and heavy
5 drinking and use.

6 I don't have time to go through each one
7 of these today, but, for example, let's use heavy
8 drinkers. Our qualitative research has shown that
9 this population takes the warning that is now on
10 the label, if you consume three or more alcoholic
11 drinks every day, very literally. In other words,
12 if they drink heavily some days, but not others,
13 there's an attitude of, that's not me.

14 This points to the need for warnings and
15 label statements to be very clear and very direct.

16 For this reason, adding the word "severe"
17 on the liver damage warning is key, not only for
18 the label, but for our educational messages as
19 well.

20 Our quantitative survey of 2,000 adults
21 will help us target specific user populations and
22 will serve as a baseline to continuously measure

1 our program's impact.

2 In the second step of the program, we'll
3 take the findings of the research and develop
4 education objectives to change how people take
5 acetaminophen. We believe this must have both
6 cognitive and behavioral objectives, and that we
7 must measure the impact of our efforts against
8 attitude and behavioral changes.

9 The third step is focused testing. While
10 we have a general idea today of what messages and
11 tools will be employed in this program, we believe
12 it is essential that all program elements,
13 including messages and tactics, be tested and
14 validated in order to increase success.

15 For example, we believe an icon on the
16 package may be a good tool to increase consumer
17 awareness of which products may contain
18 acetaminophen. Before rolling that out, however,
19 we will thoroughly test both an icon and the
20 consumer response to it. If it tests positively,
21 we will work with McNeil to incorporate their
22 efforts into our program and make it universal

1 across all OTC products. You'll hear more about
2 these efforts from McNeil later.

3 To execute our program, we will use a
4 variety of traditional and modern communication
5 tools. This will include providing immediate
6 information online to consumers and patients
7 through OTCsafety.org, and partnerships with
8 leading health resources like WebMD.

9 In stores, we will provide important
10 information about how to safely use acetaminophen
11 products right where consumers make decisions, at
12 the shelf. We'll also reach them through
13 pharmacists and at the checkout counter, as in
14 this example, a receipt handed to a purchaser of
15 an acetaminophen-containing product. And in
16 doctors' offices, clinics, hospitals, pharmacies
17 and other places where patients and healthcare
18 providers interact to reach all levels of relevant
19 patient care.

20 Materials like these will be developed
21 through our consortium and distributed to
22 healthcare providers and patients nationwide.

1 We will use our partners to multiply our
2 messages, our reach and our impact by including
3 these message tips in their material, websites,
4 consumer information and patient interaction.

5 We will work with our companies to
6 enhance the label through the use of an icon to
7 help consumers better identify and safely use
8 acetaminophen products in all -- acetaminophen in
9 all products.

10 Here is an example of an icon used to
11 help consumers identify products that do not
12 contain gluten. McNeil will speak more
13 specifically about icons in their presentation.

14 Through various media vehicles, like the
15 Internet blogs, magazines, radio and television,
16 we will reach our target audiences when and where
17 they get information. We will use targeted
18 advertising to amplify important messages, like
19 this one shown here, about the dangers of taking
20 too much acetaminophen.

21 Importantly, our messaging will include
22 specific information about liver injury, so

1 consumers know exactly how severe the risks can be
2 when they do not use the product as directed.

3 Lastly, we will continuously test and
4 evaluate our program to ensure success through
5 semi-annual repetition of the survey.

6 As mentioned earlier, the quantitative
7 survey will serve as our baseline so that we can
8 measure positive movement against our objectives.
9 Our testing in six-month intervals will allow us
10 to understand what is working and what is not so
11 that we can continuously refine as needed. Then,
12 of course, we will share our information
13 throughout with the FDA.

14 CHPA has a proven track record of
15 developing successful educational campaigns. We
16 work with partners from multi-disciplinary sectors
17 and employ the newest and most innovative
18 techniques to target consumers. One example of
19 this is our Stop Medicine [sic] Abuse Campaign
20 that we started in 2006. This comprehensive
21 campaign is addressing the intentional abuse by
22 teens of OTC cough medicines containing

1 dextromethorphan to get high. While the campaign
2 is in its early stages and still ongoing, we are
3 starting to see directional data indicating that
4 these efforts are proving effective toward
5 building awareness, shaping perceptions of risk,
6 increasing parent-teen conversations about the
7 dangers of abusing cough medicine to get high, and
8 ultimately reducing the incidence of abuse among
9 teens.

10 So, in conclusion, we recognize that
11 acetaminophen overdose is a public health concern.
12 It is one that we are taking seriously and one
13 that we believe can be only adequately addressed
14 through a comprehensive, scientifically based
15 education initiative that includes key groups from
16 both prescription and over-the-counter.

17 We are committed to carrying out such a
18 program in partnership with the FDA and other key
19 stakeholders. We support appropriate dosing
20 devices for pediatric liquid products as well as
21 dosing directions on the label for children under
22 the age of two.

1 We support continued availability of
2 1,000-milligram single doses and 4,000-milligram
3 maximum daily dose. We believe that there is a
4 clear public health benefit of over-the-counter
5 combination products containing acetaminophen and
6 we look forward to working with the FDA on this
7 important issue. Thank you.

8 DR. NELSON: Thank you. Our next speaker
9 will be Dr. Richard Dart from the Rocky Mountain
10 Poison and Drug Center.

11 DR. DART: Good morning, and thank you
12 for the opportunity to speak today. My name is
13 Rick Dart. I'm a clinical pharmacologist and
14 toxicologist and director of Rocky Mountain Poison
15 and Drug Center in Denver. I'm proud to say that
16 Rocky Mountain has published over 100 articles on
17 acetaminophen toxicity and its treatment.

18 We've addressed several issues at Rocky
19 Mountain. Most of these were the pivotal studies
20 on acetylcysteine for oral and intravenous use,
21 but in the last 10 to 15 years we've focused on
22 the safety of acetaminophen, particularly in

1 populations that are presumably susceptible to
2 acetaminophen toxicity.

3 Unfortunately, this information was not
4 noted in the FDA's discussion in the briefing
5 document, so I'd like to spend a few minutes
6 bringing this up to date.

7 Before beginning, I want to make a couple
8 of notes. First, some of the research was
9 sponsored by McNeil in the form of
10 investigator-initiated grant support. As a public
11 employee, I have no personal relationship with any
12 pharmaceutical company, including McNeil, and my
13 participation today, travel, time and preparation,
14 is not funded and my remarks do not endorse the
15 positions of any other participant in the meeting.

16 The reason to address the safety of
17 acetaminophen is because case report and registry
18 studies, such as the Acute Liver Failure Network,
19 allege that severe liver injury may occur at or
20 near the therapeutic dosage.

21 But we have to understand, as we go
22 through this information, that there are several

1 factors that foster underestimation of the dose in
2 patients that are in the clinical system.

3 First, for those of us that actually
4 treat patients, especially under an acute
5 situation, such as an acute illness, we have to
6 realize that the history is not often verified in
7 medicine. We are focused on treating the patient,
8 and once we know that the likely diagnosis may
9 involve acetaminophen, we focus on the treatment,
10 not on verifying the precise dose.

11 Other problems include the serious social
12 and financial consequences of patients that admit
13 self-harm, and this affects not only the patient.
14 Many clinicians explicitly refuse to write suicide
15 or self-harm in their records because this may
16 render the patient uninsurable in the future.

17 I've personally treated many such
18 patients who change their history when a
19 systematic history was taken after the acute
20 health episode was over.

21 In the case of fulminant hepatic failure,
22 the patient, by definition, also has altered

1 mental status. This makes a reliable history even
2 more difficult to obtain. And getting that
3 history from a friend or family member simply
4 transfers the same challenges to another person.

5 As the briefing document says, a lot of
6 Americans use acetaminophen, easily more than 100
7 million users annually in the United States.
8 These users can be divided into children and
9 adults. Each of these categories can involve a
10 single ingestion of acetaminophen or repeated
11 ingestion. I'm going to focus on the topic that
12 Rocky Mountain has focused on for the last 10 to
13 15 years, the safety of acetaminophen in adult
14 repeated ingestion.

15 An adult repeated ingestion typically
16 involves either self-treatment of pain or
17 substance abuse. How big a problem is this?
18 Well, the briefing document estimates that
19 about -- predicts 458 deaths per year based on a
20 FDA analysis. The Acute Liver Failure Network has
21 reported that roughly half, or 48 percent, of
22 these cases involve repeated doses. And that

1 produces about 220 deaths associated with repeated
2 dosing.

3 It's important to note that the ALF
4 network also reports that about two-thirds of
5 these cases, of repeated dosing, involve an
6 opioid/acetaminophen combination, which means that
7 it must be a prescription product. And about
8 one-third, or 81 of the cases, would involve a
9 single-ingredient acetaminophen product or an OTC
10 combination.

11 The FDA has proposed changes to address
12 the opioid combinations. I'm not aware of strong
13 opposition to this recommendation, so I'm going to
14 concentrate on the single-ingredient acetaminophen
15 products.

16 In the case of acetaminophen, the
17 question is, can acetaminophen cause liver failure
18 in patients taking a therapeutic dose, 4 grams a
19 day? This question is pertinent because, as
20 previously mentioned, there was a study in JAMA by
21 Paul Watkins -- in fact, the FDA working group
22 document has called for follow-up research on

1 Paul's data. But I want to point out that there
2 is already data directly relevant to this question
3 available.

4 Paul performed a randomized blinded
5 placebo-controlled trial in 145 adults. There
6 were five arms in the study and four of those five
7 arms received acetaminophen, 4 grams per day, for
8 14 days.

9 The figure shows that many patients
10 experienced an ALT that was greater than the upper
11 limit of normal, and some had levels much greater
12 than the upper limit of normal. However, there
13 was no evidence of impaired hepatic synthesis in
14 the subjects, as evidenced by no change in the
15 subjects' bilirubin or in the international
16 normalized ratio.

17 In fact, Paul wrote in his paper,
18 However, acetaminophen clearly has a remarkable
19 safety record when taken as directed, and chronic
20 treatment with 4 grams daily has been confirmed to
21 be safe.

22 In a similar vein, the FDA draft guidance

1 for industry on drug-induced liver injury offers
2 guidelines on stopping a drug during a clinical
3 trial. This guidance embodies the concept called
4 Hy's law. This law was named for Hy Zimmerman,
5 and it states that a drug that causes both
6 increased transaminase levels and jaundice in a
7 clinical trial may cause fulminant hepatic failure
8 or death in widespread clinical use.

9 The purpose of Hy's law was to
10 distinguish benign elevation of ALT versus liver
11 injury that progresses to liver failure.

12 Data show that the rate of acute liver
13 failure appears to be about one-tenth the rate of
14 liver dysfunction found in a clinical trial. The
15 bottom line is that an increase in ALT alone is
16 unlikely to be a cause for concern, and the FDA
17 does not recommend that that drug be stopped
18 during a clinical trial.

19 This conclusion seems well-justified in
20 the case of acetaminophen. Parra, et al., gave
21 acetaminophen 2 or 4 grams per day for 28 days to
22 12 patients treated with warfarin. Five of the

1 subjects experienced an ALT above the upper limit
2 of normal, and this figure shows that the mean ALT
3 increased at the 14-day time point, but it
4 returned to normal at 28 days, despite continuing
5 acetaminophen.

6 To verify this observation, we have
7 initiated a randomized trial of 300 subjects to
8 address the subject of asymptomatic
9 transaminasemia. In this study, subjects will
10 receive acetaminophen for 16 to 40 days, depending
11 on their response. If their ALT rises while under
12 treatment, they will continue on acetaminophen,
13 unless they meet the stopping criteria outlined in
14 the FDA draft guidance. We have enrolled 90
15 patients to date. As expected, about 15 percent
16 of the subjects have experienced an ALT above the
17 upper limit of normal, and the highest value to
18 date is 200 international units per liter. All
19 patients that experienced an increase in the ALT
20 have also decreased, while continuing treatment
21 with acetaminophen, and no patient has experienced
22 symptoms or an increase in the bilirubin or INR.

1 Of course, these studies have included
2 only a few hundred patients, so we -- I'm sorry.
3 I skipped a slide.

4 Several other reports have administered
5 acetaminophen to patients for a month or more,
6 mainly patients with osteoarthritis. These
7 studies also describe increases in AST or ALT,
8 although we didn't really realize this until we
9 went back and looked at them after Paul's study.
10 But like the Parra paper, none of these reports
11 found a case of acute liver failure.

12 Of course, these studies have included
13 only a few hundred patients, so we went back to
14 look at the extensive literature on acetaminophen
15 to see if we can find other examples.

16 We systematically searched the medical
17 literature for prospective studies involving
18 acetaminophen, and we included studies of adults
19 that received repeated dosing with acetaminophen
20 for at least 24 hours. We included only studies
21 that specifically addressed safety outcomes. Each
22 study was abstracted independently by two trained

1 staff members using a structured data collection
2 form.

3 Through 2006, we have found over 400
4 articles including almost 50,000 adult patients
5 treated with acetaminophen for a mean duration of
6 six days. Nearly all subjects, or 99.4 percent,
7 had a normal ALT and no liver injury documented in
8 the record. About .6 percent mentioned some type
9 of liver enzyme elevation. There were no cases of
10 acute liver failure.

11 It's also important to realize that these
12 are not your normal healthy volunteers. Their
13 diagnosis included many of the types of metabolic
14 and vascular diseases, such as stroke, metabolic
15 syndrome, cancer and many others.

16 Overall, the data available indicate that
17 acetaminophen 4 grams per day does not produce
18 severe liver injury. However, some authors have
19 proposed high risk groups that they believe could
20 be at risk for injury at or near the therapeutic
21 dose.

22 Here I show the metabolism of

1 acetaminophen. Many investigators have concluded
2 that the primary event determining toxicity is
3 metabolism of acetaminophen to
4 N-acetyl-p-benzoquinone imine, or NAPQI. Ethanol
5 consumption has been shown to increase Cytochrome
6 2E1, thereby increasing the production of NAPQI
7 two- to three-fold. And alcoholism offers a
8 patient with both increased NAPQI production and
9 decreased glutathione. This has been shown many
10 times.

11 In short, it is the balance between the
12 rate of metabolism -- production, really, of
13 NAPQI -- and replenishment of oxidized glutathione
14 that determines whether severe liver injury will
15 occur. And the chronic alcoholic patient offers a
16 window on both of these conditions.

17 Since 1997, we have studied a total of
18 484 patients receiving acetaminophen in three
19 separate studies of alcoholic patients. All the
20 studies have been the same design. The only
21 difference is the length of treatment. One study
22 administered acetaminophen for two days, one for

1 three days and one for five days.

2 All the subjects have a history of
3 substance dependence. They are current ethanol
4 drinkers, abusers, with their most recent drinking
5 episode lasting at least seven days. This is to
6 make sure the patients are induced.

7 The INR -- I'm sorry. The ALT can be
8 increased up to 200 international units per liter
9 at entry. However, patients with decompensated
10 liver function, as evidenced by an INR above 1.5
11 are excluded.

12 The subjects then receive acetaminophen 4
13 grams per day and are monitored for 36 hours after
14 completing treatment to detect late ALT
15 elevations.

16 Each of our studies has shown the same
17 result. This slide shows the results of our most
18 recent five-day acetaminophen study. The three
19 named lines shown now show the mean ALT of all
20 subjects that received acetaminophen, the mean ALT
21 of placebo subjects and the total bilirubin of the
22 acetaminophen group.

1 As you can see, the ALT increases
2 slightly, consistent with the other reports, in
3 both the -- in the acetaminophen group and also
4 some in the placebo group. However, the bilirubin
5 goes down in alcoholic patients, despite treatment
6 with acetaminophen.

7 None of our patients has ever experienced
8 an increase in bilirubin or INR, and there have
9 been no Hy's law cases.

10 We realize that many of the patients in
11 our alcohol studies had liver disease in addition
12 to alcohol, and so I'd like to show you two
13 subgroups that we have analyzed. The top line
14 shows subjects that entered the study with an ALT
15 above the upper limit of normal. And the second
16 line shows subjects with Hepatitis C. As you can
17 see, the contour of the ALT line is remarkably
18 similar to the entire cohort of all groups.

19 The studies shown here support the more
20 detailed data I've just shown you. I won't go
21 over them individually, but our conclusion is that
22 the evidence does not support the assertion that

1 acetaminophen 4 grams per day produces liver
2 dysfunction in healthy subjects or in patients
3 with a variety of diseases, including alcohol
4 abuse or Hepatitis C.

5 As you can see, the number of subjects is
6 still small, though. Added to our studies, about
7 550 patients with some type of liver disease have
8 been treated prospectively with acetaminophen,
9 most with 4 grams per day, and to date no acute
10 liver failure cases have been reported.

11 It's also important to understand,
12 however, that acetaminophen doses greater than 4
13 grams per day have been used in many studies. For
14 example, den Hertog, et al., just reported a
15 randomized trial of acetaminophen 6 grams per day
16 for three days to stroke patients. Consistent with
17 their diagnosis, these patients had serious
18 comorbid conditions as well, including
19 hypertension, diabetes and vascular disease.

20 Despite their acute illness, the rate of
21 liver -- enzyme liver disturbance in patients
22 treated with acetaminophen were no different than

1 controls.

2 This slide lists nine additional studies
3 with results similar to den Hertog, although the
4 number of patients enrolled was lower than the 697
5 in den Hertog. Each of these studies also
6 administered acetaminophen for greater -- at a
7 dose greater than 4 grams per day and for a period
8 up to 12 days.

9 In all nine studies, safety evaluations
10 were the same in control subjects as in
11 experimental subjects and there were no liver
12 cases -- liver failure cases.

13 Now, before concluding, I'd like to also
14 briefly address protein adducts.

15 If you could please show that slide.

16 We are also studying protein adducts, and
17 I agree in general with -- in fact, Laura does the
18 assays of our protein adducts. We do the clinical
19 part; she does the assay. And I agree in general
20 with her characterization. But one of the
21 questions stimulated me to add this quickly.
22 Adducts are often portrayed as representing

1 toxicity, and that comes from the early studies in
2 animals. But all data to date really indicate
3 that what adducts show us is metabolism of
4 acetaminophen through the Cytochrome 2E1 pathway.

5 The cell death process is actually a
6 separate consideration, and in fact, the presence
7 of adducts without liver injury has been produced
8 actually in Jack Hinson's (phonetic) lab as well.

9 So I don't disagree with what Laura said,
10 but I want to try to dispel the concept that any
11 level of an adduct somehow shows that injury has
12 occurred. It infers dose, not that injury has
13 occurred.

14 Next slide.

15 This shows our data in relationship to
16 one of Laura's slides, and the point here is to
17 show, at the bottom there, in the colored lines
18 and the black line, that these are our subjects
19 who have received 4 grams per day with a variety
20 of conditions, both normal subjects and alcoholic
21 patients.

22 Next slide.

1 Thank you for allowing me to fill in some
2 of the data on acetaminophen safety. Your
3 committee is faced with a fundamental dichotomy.
4 Liver failure is alleged at or near the
5 therapeutic dose. However, all the available data
6 with higher levels of confidence, such as
7 prospective studies, have failed to detect any
8 liver failure cases or violations of Hy's law.

9 The theoretical risk of toxicity is based
10 on retrospective historical data that cannot be
11 confirmed or disproven.

12 Extensive prospective data shows no cases
13 of liver failure. And acetaminophen 6 and 8 grams
14 per day also seem to be well tolerated.

15 Taken together, the maximum recommended
16 dose of acetaminophen at 4 grams a day is
17 appropriate.

18 Thank you for your attention.

19 DR. NELSON: Thank you. I recognize that
20 we're a little bit behind, but I also recognize
21 that we need to take a little bit of a break. So
22 rather than take 15 minutes, maybe -- I propose

that we take about five minutes. I'll call you back together, and we'll reconvene. Thanks.

(A recess was taken.)

DR. NELSON: Hi. We've stretched our five-minute break into an almost 15-minute break, so it would be great if we could get started again.

Our next speaker is Dr. Edwin Kuffner who is a senior director of medical affairs at McNeil Consumer Healthcare.

DR. KUFFNER: I'm Ed Kuffner, and I'm senior director of medical affairs at McNeil Consumer Healthcare. As an emergency physician and a medical toxicologist, I've cared for many children and adults with acetaminophen overdose and managed many patients with liver injury. As a researcher, I've conducted and been involved in multiple trials investigating the safety of acetaminophen. I know, as do those with similar experience, that liver injury from acetaminophen is a complex multi-factorial issue.

We are here today because we share the

1 common goal of decreasing acetaminophen overdose
2 and preventing liver injury.

3 McNeil's presentation consists of four
4 segments. First, I'll discuss McNeil's position
5 on FDA's proposed options. Then Dr. Cathy Gelotte
6 will present efficacy data showing a clear dose
7 response with increasing doses of acetaminophen.
8 I'll return to discuss McNeil's risk mitigation
9 framework which is based upon our root cause
10 analysis. On behalf of McNeil, I will make firm
11 commitments on specific interventions. Then
12 Dr. Ken Rothman, an epidemiologist, will present
13 his analysis of the potential public health
14 effects and unintended consequences that could
15 result from any regulatory action which either
16 directly or indirectly causes patients to switch
17 from acetaminophen to other analgesics,
18 specifically NSAIDs.

19 McNeil Consumer Healthcare is the leading
20 manufacturer of over-the-counter medicines in the
21 United States. For more than 50 years, McNeil has
22 been best known for Tylenol. McNeil has a broad

1 interest in over-the-counter analgesics. In
2 addition to Tylenol, we also manufacture ibuprofen
3 under the Motrin brand and aspirin under the St.
4 Joseph's brand.

5 Because of this broad portfolio, McNeil
6 is concerned about how FDA actions or options
7 could affect the use of OTC analgesics in general,
8 and especially how switching from acetaminophen
9 could create unintended consequences.

10 Acetaminophen, when used according to the
11 over-the-counter label and taken in recommended
12 doses is both safe and effective. When used as
13 directed, acetaminophen has very few adverse
14 effects and a safety profile that is unique
15 compared to other over-the-counter analgesics as
16 well as prescription analgesics.

17 The safety and efficacy of various doses
18 of acetaminophen, including 500 milligrams, 650
19 milligrams and 1,000 milligrams have been proven
20 in clinical trials and clinical use.

21 The 1,000 single adult dose provides
22 greater efficacy and longer duration of effect

1 than lower doses. For many patients, these
2 benefits are clinically important. The
3 4,000-milligram maximum adult daily dose also
4 provides meaningful patient benefit, especially
5 for those patients with osteoarthritis.

6 Intervention should be based upon root
7 causes and narrowly tailored to prevent the
8 potential for unintended consequences. We will
9 work with FDA to refine our risk mitigation
10 framework and expand its scope to involve all
11 acetaminophen manufacturers and stakeholders,
12 including the 72 percent of the over-the-counter
13 and prescription market which McNeil is not in a
14 position to directly influence.

15 Because acetaminophen is efficacious and
16 has a unique safety profile, it is commonly
17 recommended as a first-line analgesic for patients
18 with certain medical histories. It's recommended
19 for the elderly with musculoskeletal pain, those
20 at risk for gastrointestinal bleeding and patients
21 with multiple other medical conditions, including
22 renal disease.

1 Acetaminophen is also recommended for
2 patients on aspirin heart therapy because it
3 doesn't increase the risk of gastrointestinal
4 bleeding or interfere with the cardio-protective
5 benefits of aspirin.

6 Healthcare professionals take these
7 benefits into consideration every day when they
8 recommend acetaminophen instead of other
9 over-the-counter analgesics.

10 Collectively, we share a common goal of
11 encouraging patients to use all over-the-counter
12 medicines appropriately. McNeil is committed to
13 decreasing acetaminophen overdose and preventing
14 liver injury.

15 McNeil agrees with many of the FDA
16 options, including enhanced public education, and
17 is implementing FDA's new over-the-counter
18 labeling. We disagree with FDA's options to
19 completely eliminate over-the-counter access to
20 the 1,000-milligram single adult dose and the
21 4,000-milligram maximum daily dose.

22 We share the objective of encouraging

1 patients to always use the lowest effective dose,
2 which should decrease overall acetaminophen
3 exposure.

4 McNeil is recommending changing the
5 current dosing directions on both the
6 325-milligram and 500-milligram formulations, seen
7 here on your left, from take two tablets every
8 four to six hours while symptoms last, to the
9 proposed directions shown on the right, take one
10 tablet, and if pain or fever does not respond to
11 one tablet, two tablets may be needed.

12 This dose titration model is identical to
13 the directions on the current over-the-counter
14 ibuprofen label. This significant change will
15 encourage patients to use the lowest effective
16 dose and should, therefore, decrease overall
17 acetaminophen exposure within the general
18 population.

19 This measured approach will maintain
20 over-the-counter access for those patients needing
21 higher doses, and importantly, by maintaining the
22 1,000-milligram dose, we will limit unintended

1 consequences from patients switching to NSAIDs.

2 Clinical trial data and decades of use
3 support the efficacy and safety of the
4 1,000-milligram single adult dose and the
5 4,000-milligram maximum daily dose.

6 We agree with the FDA working group
7 recommendation, adding dosing directions for
8 children under two years of age to the
9 over-the-counter label is a McNeil priority for
10 which we hope to gain this committee's support
11 today. However, we disagree with the FDA option
12 of limiting pediatric liquid formulations to a
13 single concentration.

14 During our presentation, we won't cover
15 in detail the final three options listed here, but
16 I would like to make a few brief comments. It
17 appears that unit-of-use packaging for
18 prescription acetaminophen combinations would help
19 to address some of the root causes of overdose,
20 such as the use of multiple medicines containing
21 acetaminophen at the same time.

22 There is inconsistent labeling on

1 prescription acetaminophen-containing medicines,
2 many of which contain the abbreviation APAP. Many
3 patients don't realize that their prescription
4 analgesic labeled as APAP contains acetaminophen.

5 As noted by the FDA working group, the
6 available data from the United Kingdom on limiting
7 either package size or purchase amount is
8 equivocal. If pack size restrictions are endorsed
9 by this committee and only placed on
10 over-the-counter acetaminophen, a significant
11 percentage of acetaminophen users will likely
12 switch to NSAIDs, resulting in increased
13 NSAID-related adverse effects.

14 Finally, as previously discussed by
15 Dr. Lewis, eliminating over-the-counter
16 combination acetaminophen-containing medicines
17 would also be a mistake. Decoupling medicines for
18 which there is a medical rationale which are
19 matched for dose, frequency of administration and
20 duration of clinical effect may actually lead to
21 an increase in dosing errors, overdose and adverse
22 effects.

1 Dr. Cathy Gelotte will now review the
2 efficacy data on different doses of acetaminophen.
3 Thereafter, I will return to review our risk
4 mitigation framework that is based upon a root
5 cause analysis.

6 DR. GELOTTE: Good morning. I'm Cathy
7 Gelotte, senior director of clinical pharmacology
8 at McNeil Consumer Healthcare. Today, FDA is
9 asking the committee to consider reducing the
10 maximum single dose of 1,000 milligrams and the
11 maximum dose of 4,000 milligrams.

12 Key to a discussion of the
13 1,000-milligram dose is its efficacy relative to
14 other acetaminophen doses. Additionally, any new
15 proposed maximum acetaminophen dose should be
16 understood in the context of other available OTC
17 analgesics.

18 The efficacy of acetaminophen is
19 well-established from 300 to 1,000 milligrams,
20 with data from over 110 randomized controlled
21 trials. For over 50 years, acetaminophen has
22 assumed an important role in the management of

1 pain for the general population and is the
2 preferred or first-line analgesic for people who
3 have certain health risks.

4 Clinical data outlined in this
5 presentation demonstrate that the maximum dose of
6 1,000 milligrams is more effective than the lower
7 500 and 650 doses.

8 If a decision is made to limit the
9 maximum dose to 650 milligrams, it's important to
10 note that the clinical trial data show that this
11 lower acetaminophen dose provides less pain relief
12 and has shorter duration of action than the
13 maximum OTC dose of ibuprofen.

14 This disparity in obtainable analgesic
15 effects between 650 dose and OTC ibuprofen could
16 facilitate consumer switching and become an
17 important safety concern.

18 Finally, the maximum daily dose of
19 acetaminophen, 4,000 milligrams, is effective for
20 recurrent osteoarthritis pain.

21 Before presenting clinical trial data,
22 I'd like to offer several points relevant to the

1 conduct and interpretation of analgesics clinical
2 trials. For a number of years, various clinical
3 pain models have been used by researchers and
4 accepted by FDA as reasonable surrogates to
5 generalize the acute analgesic effects of both
6 prescription and over-the-counter drugs. Efficacy
7 end points include patient reports of pain
8 intensity and pain relief.

9 The sensitivity of an analgesic model to
10 differentiating drug from placebo or to
11 demonstrate a dose response generally depends upon
12 pain severity at the time of dosing. As the level
13 of baseline pain in the study population
14 increases, the incremental benefits of a higher
15 analgesic dose becomes more evident.

16 Other important factors are the sample
17 size and underlying homogeneity of the painful
18 condition in the study population.

19 To our knowledge, there is no single
20 generally accepted definition of clinically
21 meaningful relief between treatments or doses. We
22 present one definition as a measure of clinically

1 meaningful effect in acute pain studies that some,
2 including the Cochrane review, have used. This is
3 the percent of subjects reporting more than 50
4 percent of maximum total pain relief as a specific
5 time or over the entire observation period.

6 The efficacy of a single dose of
7 acetaminophen 500 milligrams has been demonstrated
8 in placebo-controlled trials in a variety of pain
9 models listed here. There were seven studies that
10 evaluated this dose for pain following oral
11 surgery, which is a widely used analgesic model.
12 Subjects are often healthy, with few confounding
13 medical conditions, and the level of baseline pain
14 due to trauma can be relatively standardized. In
15 five of these studies, the 500-milligram dose was
16 shown effective.

17 In addition, other analgesic models have
18 demonstrated a significant effect of 500
19 milligrams compared with placebo.

20 Results for one of these studies is shown
21 here, where 500 milligrams was evaluated in adults
22 and adolescents, with pain following

1 tonsillectomy. As you can see on the left, this
2 dose provided significantly greater relief
3 compared with placebo from one to four hours of
4 the observation period. At the end of this
5 period, subjects were asked to provide a global
6 assessment of treatment. As shown on the right,
7 most subjects given acetaminophen rated their
8 treatment as excellent or good, whereas most
9 subjects given placebo rated their treatment as
10 fair or none.

11 From the review of the literature and
12 McNeil's internal database, we found three
13 clinical studies conducted over the last ten years
14 that compared both the 500- and 1,000-milligram
15 doses.

16 In a tension headache model, Steiner
17 found that the 1,000-milligram dose was
18 significantly better than placebo and numerically
19 greater than 500, which did not separate from
20 placebo.

21 Study 02-156 used the dental impaction
22 model and the Bachert study enrolled subjects with

1 fever associated with an adult respiratory
2 illness. These studies demonstrate that both
3 acetaminophen doses were effective and that 1,000
4 milligrams was significantly more effective than
5 500.

6 As noted earlier, we chose the definition
7 of a clinically meaningful effect as the percent
8 of subjects reporting more than 50 percent of
9 maximum total pain relief. Shown here is the
10 proportion of subjects in each treatment group in
11 study 02-156 that reported this level of relief
12 from dental pain. More than half of the subjects
13 treated with acetaminophen 1,000 milligrams met
14 this criterion, compared to one-third among those
15 receiving 500 and one-fourth receiving placebo.
16 The 20 percentage point difference between active
17 treatment groups is important. This difference
18 helps illustrate the real-world concept that a
19 consumer can obtain benefit with a single
20 500-milligram dose and, if needed, there is an
21 additional analgesic benefit that can be afforded
22 by the 1,000-milligram dose.

1 And antipyretic dose response has also
2 been shown for acetaminophen in adults with
3 febrile upper respiratory illness. This figure is
4 taken from the study by Bachert and shows the time
5 course of orally measured body temperature over
6 six hours. Both acetaminophen doses were superior
7 to placebo, and the 1,000-milligram dose provided
8 significant maximum reduction in oral temperature
9 compared with 500 milligrams.

10 Although a large number of clinical
11 trials have individually evaluated the efficacy of
12 either 1,000 or 650 milligrams acetaminophen, we
13 are aware of eight placebo-controlled trials that
14 compared both doses directly in the same study.
15 These include episiotomy pain studies from the
16 original NDA approved in 1975, and subsequent
17 dental pain studies in patients with more severe
18 pain.

19 In materials submitted by FDA to the
20 committee, it has been suggested that there is
21 little difference in effectiveness between these
22 doses. Based on analgesic dose response in

1 general and the types of pain models used to
2 demonstrate efficacy, we believe the study data
3 show that the 1,000-milligram dose provides
4 clinically meaningful pain relief to a greater
5 percentage of subjects.

6 This table summarizes the studies
7 submitted in the original NDA that compared the
8 efficacy of both doses in post-partum episiotomy
9 pain. The first two studies were inconclusive, as
10 there was no treatment effect. The studies by
11 Dr. Hopkinson and Bare demonstrate the
12 1,000-milligram dose was superior to the 650 dose.
13 The last study was terminated early due to slow
14 enrollment, although the data were later pooled
15 with the positive studies and published by
16 Hopkinson and colleagues.

17 Shown here are the time action curves for
18 the Hopkinson study on the left and the Bare study
19 on the right. Differences in pain intensity from
20 baseline were evaluated up to four hours after a
21 single dose.

22 We see, from these clinical data that the

1 differences in pain intensity are greater for the
2 1,000-milligram dose. Although not shown here,
3 other pain measurements were significantly greater
4 for 1,000 versus 650 in both studies.

5 This figure is taken from the data in the
6 Hopkinson's publication and shows the cumulative
7 proportion of subjects who reported more than 50
8 percent of the maximum pain relief over four
9 hours. Of note is the 24 percentage point
10 difference in response between the 1,000-milligram
11 and 650-milligram doses in this study.

12 This difference is similar to the 20
13 percentage point difference between the 1,000 and
14 500-milligram doses shown earlier in the dental
15 study 02-156.

16 In the early 1980s, the efficacy of 1,000
17 and 650 acetaminophen was also compared in oral
18 surgery models outlined in this table. Third
19 molar dental impaction surgery is the preferred
20 model to evaluate a drug's dose response curve.
21 Results of these earlier studies are consistent
22 with our current understanding that more severe

1 pain is needed at baseline for assay sensitivity.

2 In study 80-214 which enrolled 58 percent
3 subjects with severe pain, the 1,000-milligram
4 dose was superior to 650 for one pain measure and
5 numerically greater for the remaining end points.
6 These results may reflect the heterogeneous
7 surgical procedures as, today, only one procedure
8 is typically used.

9 In study 80-224, the number of subjects
10 per group was too small for a subgroup analysis,
11 with only six subjects having severe pain.

12 Study 80-223 enrolled subjects after
13 third molar impaction surgery. The
14 1,000-milligram dose demonstrated greater efficacy
15 than 650 in the cohort of subjects with more
16 severe pain for global assessment by subjects, and
17 approached significance for several pain measures.

18 On the left, the time action curve from
19 study 80-223 shows that subjects treated with
20 1,000 milligrams had more pain relief than
21 subjects treated with 650 or placebo.
22 Additionally, the 1,000-milligram dose provided

1 significantly higher maximum pain relief than both
2 650 and placebo over the four-hour observation
3 period.

4 One measure of analgesic duration is the
5 number of hours that subjects report that pain is
6 half gone. As shown on the right, subjects
7 receiving 1,000 milligrams had significantly more
8 hours with pain half gone compared with placebo.
9 This dose was also numerically better than 650
10 milligrams, and the difference approached
11 statistical significance.

12 We also reviewed the literature and
13 internal McNeil database for placebo-controlled
14 studies that compared single doses of
15 acetaminophen 600 or 650 milligrams to the maximum
16 OTC dose of ibuprofen. In two dental impaction
17 studies by Cooper and Forbes, both active
18 treatments were significantly better than placebo
19 in providing pain relief. However, ibuprofen 400
20 was significantly better than acetaminophen 600.

21 Three dental pain studies were conducted
22 by our pharmaceutical division as part of the

1 development program of a tramadol combination
2 product. All three studies demonstrated that
3 ibuprofen 400 milligrams was more effective and
4 had a longer duration than acetaminophen 650
5 milligrams.

6 This figure summarizes the percentage of
7 subjects who obtained more than 50 percent maximum
8 pain relief for each of the three dental pain
9 studies. From these results, we see that
10 ibuprofen 400 milligrams provided clinically
11 meaningful relief for 16 to 28 percent more
12 subjects compared with acetaminophen 650.

13 In the published study by Forbes and
14 colleagues, the percent of subjects with more than
15 50 percent pain relief was measured from one to
16 six hours. You can see that more subjects
17 obtained greater pain relief with the 400
18 ibuprofen dose. Data from these five studies
19 comparing both analgesics suggest that some
20 individuals would not achieve adequate pain relief
21 with the lower acetaminophen dose. Adequate
22 analgesia is a clinically appropriate goal to

1 which consumers will likely self-titrate.

2 If FDA were to limit the acetaminophen
3 dose to 650 milligrams, some consumers for whom
4 acetaminophen is the most appropriate analgesic
5 may move instead to greater pain relief offered by
6 the maximum OTC dose of ibuprofen.

7 An important use of acetaminophen is to
8 treat recurrent osteoarthritis pain. Recently,
9 McNeil sponsored a randomized placebo-controlled
10 study having a standard design per FDA's guidance
11 on osteoarthritis trials that evaluated two doses
12 of acetaminophen. This 12-week study evaluated
13 doses of 3900 and 1950 milligrams in subjects with
14 knee and hip osteoarthritis.

15 Shown here are the results for the three
16 primary end points of this trial. They are the
17 average change from baseline through week 12 for
18 the WOMAC scores for pain and for physical
19 function and the subjects' global assessment of
20 therapy.

21 Acetaminophen 3900 milligrams per day was
22 significantly better than placebo for all three

1 end points, whereas acetaminophen 1950 milligrams
2 per day was significantly better than placebo for
3 only one end point, the subject's global
4 assessment. Consistent with other published
5 trials, these data demonstrate the beneficial
6 effect of the maximum daily dose in subjects with
7 osteoarthritis pain. The data also show a more
8 modest effect in subjects taking 1950 milligrams
9 per day.

10 In summary, acetaminophen efficacy is
11 well-established for doses from 325 to 1,000
12 milligrams in placebo-controlled trials. Clinical
13 data demonstrate that the maximum single dose of
14 acetaminophen, 1,000 milligrams, provides more
15 effective pain relief compared with the lower 500
16 and 650-milligram doses.

17 Given that painful conditions are
18 widespread in the population, adequate analgesia
19 is an appropriate goal for the majority of
20 consumers.

21 Current data show that the 650-milligram
22 acetaminophen dose provides less effective pain

1 relief than the maximum doses of other available
2 OTC analgesics.

3 Consumers, without having adequate
4 choices for optimal effectiveness, may choose the
5 analgesic medicine that provides the greatest pain
6 relief instead of that most appropriate for them
7 and their condition.

8 Finally, the maximum daily dose of
9 acetaminophen effectively relieves mild to
10 moderate osteoarthritis pain.

11 I'd like to welcome back Dr. Kuffner.

12 DR. KUFFNER: I'd now like to discuss
13 McNeil's risk mitigation framework. The framework
14 is designed to meet our common goal of reducing
15 acetaminophen overdose and preventing liver
16 injury. It also preserves over-the-counter access
17 to formulations and doses and minimizes the risk
18 of acetaminophen users switching to NSAIDs.

19 Prior to designing the risk mitigation
20 framework, we performed a case level review of our
21 company post-marketing database to better
22 understand root causes of acetaminophen overdose.

1 This review spanned five years of U.S. data for
2 both children and adults with a focus on moderate
3 to severe and fatal hepatic events.

4 We confirmed common root causes across
5 over-the-counter and prescription medicines and
6 across pediatric and adult age groups. This
7 allowed us to categorize reports based upon a
8 number of different factors, including the
9 reported medicine involved, the age of the
10 patient, the reported intent for ingesting or
11 administering the medicine, the severity of the
12 reported clinical effects, and the reported dose
13 ingested.

14 Our root cause analysis identified the
15 most significant behaviors leading to overdose. I
16 will summarize these important root causes and
17 then, one by one, outline McNeil's recommended
18 interventions.

19 In adults, most overdose cases resulting
20 from a medication error involved taking more than
21 the labeled dose or dosing too often.

22 Another important root cause in

1 medication errors involved taking multiple
2 acetaminophen-containing medicines at the same
3 time.

4 In addition to medication errors, there
5 are many cases of adults intentionally overdosing
6 in an attempt to truly harm themselves or as part
7 of a suicide gesture.

8 In children, by far the greatest number
9 of exposures were accidental unsupervised
10 ingestions occurring when curious young children
11 access medicines that are not kept out of their
12 reach. Similar to what we saw in adults, most of
13 the medication errors involved caregivers giving
14 children more than the recommended dose or dosing
15 too frequently.

16 Using multiple acetaminophen-containing
17 medicines at the same time was also a root cause
18 identified in the pediatric cases.

19 Unique to children, there were cases
20 where caregiver confusion was reported. Some of
21 these reports involve the infants' concentrated
22 formulation, and within these reports, a number of

1 different contributing factors were identified.

2 A detailed case level review of these
3 reports does not suggest that the root cause of
4 these medication errors is as simple as caregivers
5 not knowing the difference between the more
6 concentrated infants' formulation and the less
7 concentrated children's formulation. There were
8 also occasions where adult medications were given
9 to children.

10 I will like to first discuss our risk
11 mitigation strategy for reducing the first
12 category of root causes, adult medication errors.

13 As we discussed earlier, we are proposing
14 changing the dosing directions on adult
15 acetaminophen-containing medicines to promote the
16 importance of always using the lowest effective
17 dose.

18 We are recommending changing the dosing
19 directions from take two tablets to take one
20 tablet, and if pain or fever does not respond to
21 one tablet, two tablets may be needed. Using the
22 lowest effective dose will help reduce the overall

1 acetaminophen exposure across the general
2 population while maintaining access for those
3 patients who need the 1,000-milligram dose and
4 minimizing unintended consequences from patients
5 switching to NSAIDs.

6 Another source of medication errors come
7 from patients using multiple medicines that
8 contain acetaminophen at the same time. As
9 discussed earlier by Dr. Suydam, icons and
10 pictograms have been demonstrated to reduce
11 medication errors by enhancing written directions
12 and dosing information. Icons and pictograms have
13 to potential to heighten patient and caregiver
14 awareness of active ingredients, dosing directions
15 and other warning. Icon and pictogram development
16 is under way, and we are following a rigorous
17 process.

18 We want to ensure that
19 acetaminophen-related icons and pictograms most
20 effectively communicate the intended information
21 and are suitable for both over-the-counter and
22 prescription use.

1 We are not proposing these specific icons
2 today, but these are examples of how icons or
3 pictograms may be able to communicate
4 acetaminophen as an ingredient and the maximum
5 adult daily dose.

6 If icons being tested by McNeil are
7 demonstrated to enhance written label
8 instructions, we would work with FDA and other
9 stakeholders to incorporate them into the Drug
10 Facts label on all over-the-counter medicines. We
11 would also work with the prescription
12 manufacturers and other stakeholders to have the
13 icon included on all prescription
14 acetaminophen-containing medicines.

15 Finally, in an attempt to further reduce
16 medication errors, we're testing package
17 innovations that reinforce key messages at the
18 point of use, such as not taking more than the
19 maximum adult daily dose. Obviously the specific
20 wording will need to be tested to ensure patients
21 and consumers understand the message.

22 The majority of adult cases of

1 acetaminophen overdose and liver injury are the
2 result of intentional self-harm ingestions.
3 Patients who attempt to harm themselves can be
4 broadly divided into two groups, a group of truly
5 suicidal patients who really intend to hurt
6 themselves, and a group of patients who make an
7 impulsive suicide gesture.

8 Many patients making a suicide gesture
9 will impulsively turn to the most easily
10 accessible means. The literature shows that
11 approximately 50 percent of suicide attempts are
12 impulsive and that even small impediments may
13 actually deter people from using a specific
14 method.

15 In addition to preventing medication
16 errors, flow restrictors in the form of
17 modifications to the packaging to reduce the
18 bottle opening and limit the flow of medication
19 from the container also have the potential to
20 prevent or limit the magnitude of impulsive
21 self-harm ingestions.

22 If research indicates that flow

1 restrictors on adult medicines may be effective in
2 reducing self-harm or medication errors while not
3 deterring appropriate use, McNeil would begin
4 placing flow restrictors on all adult
5 acetaminophen-containing medicines.

6 Our risk mitigation framework also
7 addresses pediatric accidental, unsupervised
8 ingestions. Here you see pediatric exposure data
9 segmented by intent. In children, accidental,
10 unsupervised ingestions are the most common root
11 cause of exposures to both over-the-counter and
12 prescription medicines, as demonstrated by data
13 from the CDC on your left, and to acetaminophen,
14 as demonstrated by data from the American
15 Association of Poison Control Centers on your
16 right.

17 Despite long-standing "keep out of the
18 reach of children" campaigns by multiple
19 stakeholders, including McNeil, reports of
20 accidental, unsupervised ingestions continue to be
21 a root cause identified within our company
22 post-marketing safety database.

1 Recently, we recontacted caregivers who
2 reported an accidental, unsupervised ingestion of
3 an over-the-counter medicine to our call center to
4 better understand contributing factors. Some of
5 the findings were not new. Most accidental,
6 unsupervised ingestions occur in young children,
7 and they occur in the home. Interestingly, most
8 occurred when the medication was temporarily
9 removed from its normal storage location and left
10 out after treating a sick child.

11 Accidental, unsupervised ingestions were
12 more common within 24 hours of the last
13 therapeutic use of the medicine. Many times, the
14 child who had the accidental, unsupervised
15 ingestion was the same child to whom the caregiver
16 administered the same medicine.

17 We have been pursuing packaging
18 innovations that add additional passive
19 protection. We want to limit exposures in cases
20 where children defeat the child-resistant features
21 or when caregivers don't properly reapply or
22 reengage them. McNeil is adding flow restrictors

1 to all of our pediatric liquid
2 acetaminophen-containing medicines. Specifically,
3 a press-in bottle adaptor will be added to all
4 concentrated infants' Tylenol drops to prevent
5 children from accessing the medicine.

6 Since the medicine needs to be accessed
7 with an oral syringe, this innovation also has the
8 potential to increase caregiver use of the
9 product-specific dosing device and decrease
10 medication errors.

11 A similar type of flow restrictor will be
12 added to all children's liquid Tylenol medicines.
13 This flow restrictor is designed to be used with a
14 dosing cup, which is the preferred way that
15 caregivers dose older children. Pressure needs to
16 be applied to the rigid plastic in order to
17 squeeze out the medicine.

18 Flow restrictors on all liquid pediatric
19 acetaminophen-containing medicines will certainly
20 decrease accidental, unsupervised ingestions and
21 limit the magnitude of exposures.

22 Approximately 70 percent of accidental,

1 unsupervised ingestions occur with pediatric
2 medicines. All of McNeil pediatric
3 acetaminophen-containing medicines currently have
4 child-resistant closures. In order to potentially
5 further reduce accidental, unsupervised
6 ingestions, McNeil will eliminate all
7 non-child-resistant packaging across all
8 acetaminophen-containing adult medicines. New
9 packages will be in distribution in 2010.

10 In children, most medication errors
11 leading to overdose and liver injury involve
12 caregivers administering more than the recommended
13 dose.

14 This table reports overdose that led to
15 moderate or severe and fatal liver injury in
16 children. Approximately 75 percent of liver
17 injury occurs in children less than two years of
18 age. It's important to note that there's no
19 dosing information on the over-the-counter label
20 for children under two years of age. It's not a
21 coincidence that most liver injury occurs in the
22 age group where there's no dosing information on

1 the over-the-counter label.

2 From the case level review, it's often
3 difficult to determine why an overdose occurred,
4 but there are clues in other data.

5 Because McNeil manufactures both Tylenol
6 and Motrin, we have the unique ability to compare
7 data across ingredients. As you see from this
8 data, regulatory decisions that impact one
9 over-the-counter analgesic can significantly
10 impact others. On this slide, you see the number
11 of dosing inquiries received by our call center
12 from caregivers for pediatric Tylenol medicines in
13 red and for pediatric Motrin medicines in yellow.
14 The volume of dosing units for pediatric Tylenol
15 and pediatric Motrin medicines distributed each
16 year is similar.

17 On your left, the graphs represent
18 inquiries regarding children two to less than 12
19 years of age where there is dosing information on
20 the over-the-counter label for both Tylenol and
21 Motrin. You see a similar number of dosing
22 inquiries.

1 On your right, the graphs represent
2 inquiries for children less than two years of age
3 where there is dosing information on the pediatric
4 Motrin label, but no dosing information on the
5 over-the-counter label for pediatric Tylenol.

6 Our call center receives many more dosing
7 inquiries from caregivers for pediatric Tylenol
8 where there is no dosing information on the
9 over-the-counter label.

10 McNeil will further differentiate the
11 labeling between concentrated Tylenol infants'
12 drops and children's Tylenol. On the left you see
13 the current packaging. On the right you see our
14 proposed packaging which further differentiates
15 the two formulations. This new packaging will
16 begin distribution in 2010.

17 Our work on icons and pictograms may also
18 help to decrease pediatric medication errors.
19 Icons and pictograms can help identify
20 acetaminophen as an active ingredient, visually
21 communicate dosing information and reinforce that
22 adult medicines should never be given to children.

1 If tested to be effective, icons and
2 pictograms will be placed on both adult and
3 pediatric medicines.

4 It's critical that the impact from
5 changes to packaging, labeling and education be
6 measured closely. Where data gaps exist, McNeil
7 is committed to supporting scientific research and
8 surveillance designed to provide additional data
9 and enhance our understanding of acetaminophen
10 overdose and liver injury.

11 McNeil agrees with FDA that there are
12 opportunities for manufacturers, regulators and
13 healthcare providers to better understand root
14 causes of acetaminophen overdose and liver injury.

15 There is also an opportunity to augment
16 current surveillance systems. McNeil will work
17 collaboratively with FDA, with over-the-counter
18 and prescription manufacturers, public health
19 agencies, healthcare professionals and others to
20 enhance data collection tools in order to better
21 understand patient behaviors and potential other
22 risk factors that may lead to acetaminophen

1 overdose and liver injury. Surveillance systems
2 should be designed to seek out cases and
3 systematically gather and record information in a
4 transparent fashion.

5 Data collection systems must use clear
6 and consistent definitions to accurately define
7 and collect key information for evaluating root
8 causes, such as patient characteristics, products
9 involved, intent and indications for use. It's
10 also important that, with each case, we attempt to
11 understand as best we can the actual dose ingested
12 or administered, and the duration of use.

13 Realistic yet aggressive goals must be
14 set for measuring the impact of interventions on
15 patient understanding, medicating behaviors in
16 acetaminophen overdose and liver injury. Some
17 metrics we propose include establishing a baseline
18 and tracking the number of reports documented by
19 poison centers, emergency departments and within
20 our own company post-marketing database. Changes
21 in both the number of cases, the magnitude of
22 exposures and the seriousness of the adverse

1 events should be tracked.

2 In addition, we will examine consumer
3 panel data to better understand how the
4 multi-faceted interventions change patient and
5 caregiver attitudes and behaviors, such as taking
6 more than the recommended dose or using multiple
7 medicines that contain acetaminophen at the same
8 time.

9 And when it comes to impulsive self-harm,
10 we could look at the number of cases and the
11 magnitude of the exposures and the severity of
12 liver injury. Obviously, if McNeil were to be the
13 only acetaminophen manufacturer to implement the
14 proposed package and label changes, it will be
15 more difficult to make a significant impact on
16 acetaminophen overdose and liver injury.
17 Therefore, we advocate that this be adopted on an
18 industry-wide basis.

19 McNeil is funding research into patients'
20 understanding of over-the-counter analgesic Drug
21 Facts labeling and the awareness of using
22 over-the-counter acetaminophen-containing

1 medicines with prescription medicines that also
2 contain acetaminophen. One study will explore
3 common causes for misunderstanding the
4 over-the-counter Drug Facts label and may provide
5 insights into patient characteristics such as
6 socioeconomic status, literacy levels and
7 experience with OTC analgesics and how they affect
8 the potential for medication errors.

9 A second study will explore patient
10 understanding of the presence of acetaminophen in
11 prescription acetaminophen medicines and how
12 healthcare providers communicate warnings to
13 patients following discharge from the emergency
14 department.

15 Results of these important studies will
16 help guide future interventions.

17 In summary, McNeil is committed to
18 working with FDA, to the members of this committee
19 and others to decrease acetaminophen overdose and
20 liver injury. Today we have proposed options that
21 we believe will accomplish this shared goal in a
22 way that maintains access to important doses and

1 formulations that are used safely and
2 appropriately by the vast majority of patients and
3 caregivers and do not create unintended
4 consequences.

5 There are three areas in which McNeil's
6 options differ from those proposed by the FDA.
7 First, as previously discussed by Dr. Lewis,
8 eliminating over-the-counter
9 acetaminophen-containing combination medicines
10 would be a mistake. Decoupling medicines for
11 which there is a medical rationale which are
12 matched for dose, frequency of administration and
13 duration of clinical effect may actually lead to
14 an increase in dosing errors, overdose and adverse
15 events.

16 McNeil is a key participant in the new
17 industry education program, as outlined by
18 Dr. Suydam. We believe implementing effective
19 icons and pictograms should reduce the use of
20 multiple acetaminophen-containing medicines at the
21 same time.

22 McNeil disagrees with the FDA option to

1 eliminate the infants' concentrated formulation.
2 This formulation helps caregivers more easily dose
3 young children, and is the form that's most
4 recommended by pediatricians for children under
5 two years of age. Adding flow restrictors on all
6 pediatric liquid acetaminophen-containing
7 medicines and further differentiating packaging
8 between the different products should reduce
9 overdose and liver injury.

10 If this committee and the FDA truly want
11 to decrease medication errors leading to overdose
12 in children, the single most impactful measure
13 would be to add dosing information to the
14 over-the-counter label of acetaminophen-containing
15 medicines for children under two years of age.

16 To encourage the use of the lowest
17 effective dose while avoiding unintended
18 consequences, McNeil proposes changing the dosing
19 directions to take one tablet every four to six
20 hours while symptoms persist and, if pain or fever
21 does not respond to one tablet, two tablets may be
22 used.

1 Some of the FDA options may engender
2 unintended health consequences, specifically
3 limiting access to the 1,000-milligram dose will
4 lead to inadequate relief for patients with more
5 significant pain. Lack of access to the
6 4,000-milligram maximum daily dose will also lead
7 to inadequate analgesic, especially for patients
8 with osteoarthritis pain.

9 Dose restrictions and selective package
10 size limitations have the potential to shift
11 patients and consumers to less safe alternatives.
12 Dr. Ken Rothman will now put the potential health
13 consequences related to switching into context.

14 DR. ROTHMAN: Good morning. My name is
15 Ken Rothman. I'm an epidemiologist. I work for
16 the Research Triangle Institute. I was invited to
17 speak today by McNeil Consumer Healthcare. McNeil
18 has a contract with RTI to pay for my time working
19 on the question of switching.

20 I'm here today to describe some
21 calculations that project the change in the number
22 of fatal adverse outcomes if people who are using

1 acetaminophen would switch to using NSAIDs.

2 Here is the specific question that I
3 addressed: What would be the net change in the
4 number of deaths from adverse effects if some
5 people who currently use acetaminophen switched to
6 NSAIDs? That is, assuming that some people will
7 switch, what are the consequences of switching?

8 To do this calculation, I used data from
9 several different sources. I used U.S. census
10 projections to estimate the current size of the
11 U.S. population. I used mortality data from U.S.
12 vital statistics, which are based on the
13 compilation of death certificate information. I
14 needed data on the usage of acetaminophen and
15 NSAIDs, both of which are available
16 over-the-counter and by prescription. And this
17 information was obtained from research conducted
18 by the Slone Epidemiology Center located at Boston
19 University.

20 The calculation also required information
21 on the strength of association between
22 acetaminophen and NSAIDs and their primary adverse

1 effects. These adverse effects were, as a group,
2 acute liver failure, acute renal failure and upper
3 GI bleeding. This information was taken from
4 published epidemiologic studies that have been
5 reported, a combination of cohort studies and
6 case-controlled studies.

7 One source of data that could not be used
8 is data from case series. Many reports of case
9 series have been published and have received
10 attention, but these data are not very useful to
11 epidemiologists for several reasons. First, data
12 on cases alone do not allow any estimates of
13 association between possible cause and effect
14 because they do not involve comparison with a
15 control group.

16 Case series are typically compiled from
17 referred cases. These referrals come from
18 populations that are not well-defined. And,
19 furthermore, the referral of cases could be
20 influenced by the presence of the exposures of
21 interest themselves.

22 For these reasons, we restricted our

1 study -- our calculations to formal epidemiologic
2 studies.

3 In this exercise, I focused on the net
4 change in the number of deaths. I haven't
5 considered morbidity.

6 For every patient who dies from an
7 adverse effect, there are many more who suffer
8 morbidity but survive. So the focus on mortality
9 is an underestimate of the total effect that
10 switching might have on a population.

11 Whatever the results of switching, they
12 are proportional to the number of people who do
13 switch. For example, the change in the number of
14 deaths that would occur if 10 percent of people
15 switched would be half the change that would occur
16 if 20 percent switched.

17 I restricted the calculation to
18 projections for the U.S. adult population. The
19 Slone survey that I mentioned before reports that
20 22 percent of adults used at least one dose of an
21 NSAID during the previous week. The corresponding
22 figure for acetaminophen was 18 percent. The

1 Slone survey also reported that 0.4 percent of
2 acetaminophen users took more than 4 grams a day.

3 These latter data were useful because the
4 effect of acetaminophen on acute liver failure is
5 thought to be extremely different for people who
6 use it in excess dosage.

7 The calculations assume that any
8 switching from acetaminophen to NSAIDs is
9 independent of acetaminophen dose.

10 Here I show, for 2005, the number of
11 deaths in adults for which acute liver failure was
12 listed as the underlying cause of death on the
13 death certificate. 2005 is the most recent year
14 for which this number was available. Based on the
15 U.S. adult population in 2005, the risk of dying
16 with acute liver failure listed as the underlying
17 cause on the death certificate was 3.5 per
18 million.

19 If we also counted deaths for which these
20 outcomes -- acute liver failure -- was listed as a
21 contributing cause of death, the risks are much
22 greater as you can see on the right-hand part of

1 this slide.

2 Counting those additional deaths
3 increases the risk for the range of outcomes
4 studied by roughly four to eight times. Using
5 only the underlying cause underestimates the
6 deaths of interest from the public health's
7 perspective. But counting both underlying and
8 contributing causes of death could overestimate
9 the number of deaths that would be of interest.
10 Giving both is a reasonable way to bracket the
11 projects and get an idea of the range of values
12 that might occur.

13 On this slide I show the data for renal
14 failure for which the risk based on underlying
15 cause of death is 34.7 per million. And on the
16 next row I show the data for GI bleeding, for
17 which the risk is 43 per million based on
18 underlying cause.

19 Note that the risk of dying from acute
20 liver failure is much lower than the risk of dying
21 from either acute renal failure or GI bleeding.
22 And I emphasize these are total population risks

1 for the U.S. population.

2 As I indicated a moment ago, we combined
3 these risk estimates that you just saw with data
4 on the prevalence of drug use and estimates of the
5 association between drugs and the end points of
6 concern which were taken from the epidemiologic
7 literature. The epidemiologic literature, of
8 course, gives a range of values for the strength
9 of association of each agent with the outcomes
10 that we're interested in.

11 Based on the literature, I chose one
12 value as illustrative to anchor the calculations,
13 but I used a range of possible values for the
14 strength of association, to examine the
15 sensitivity of the calculation to each of the
16 values that we used.

17 This slide shows the illustrative value
18 and also the range of relative risk values that
19 was considered for the effect of NSAIDs of each of
20 these three outcome categories.

21 Consider, for example, acute liver
22 failure. The literature largely indicates that

1 use of NSAIDs is not associated with acute liver
2 failure. But not all studies report a lack of
3 association. I used no association -- that is,
4 the relative risk of 1.0 -- for the illustrative
5 calculation. But for the sensitivity analyses, I
6 allowed that the effect of NSAIDs could range as
7 high as a 2.8-fold increase in risk for acute
8 liver failure.

9 For GI bleeding, I considered a range of
10 relative risks from a low of 2 to an upper level
11 of 5, but I used a value of 3.7 for the
12 illustrative computation.

13 On this slide I show the corresponding
14 values for the relative risk from the use of
15 acetaminophen. For acetaminophen, I used two
16 subsets of users, one corresponding to use within
17 the recommended dose levels, and the other being
18 those who use acetaminophen in excess of the
19 recommended levels. The reason for this
20 distinction, as I mentioned, is that acute liver
21 failure is thought to result only when
22 acetaminophen is used at excess doses.

1 Nevertheless, the range of effects that I
2 used for the therapeutic levels did allow for a
3 slight increase in risk for acute liver failure.

4 The epidemiologic literature provides
5 little help regarding the magnitude of the
6 association between excess acetaminophen use and
7 the occurrence of acute liver failure. I have
8 assumed that the association is extremely strong,
9 and I have employed a range of effects that go
10 from 10-fold up to 200-fold. I also allowed for
11 moderate effects of acetaminophen on GI bleeding
12 and on acute renal failure, particularly among
13 those using it above recommended doses.

14 From that input data, I then projected
15 how many deaths would occur among the current U.S.
16 adult population under various switching
17 scenarios. This slide presents the results based
18 on the underlying cause of death.

19 For example, suppose 20 percent of
20 acetaminophen users switched to using NSAIDs.
21 Then I project that there would be an increase of
22 656 deaths each year. That's based on the

1 illustrative values that I indicated on the
2 previous slides.

3 If 10 percent switched, that number would
4 be halved. There would be an increase of 328
5 deaths.

6 On the right-hand column, I give a range
7 of results, and this range reflects the ranges of
8 values that were used for these relative risks,
9 relating acetaminophen and NSAIDs to the three
10 adverse outcomes. These ranges show the degree to
11 which these results are sensitive to these assumed
12 effect levels. They indicate that there would be
13 an increase of deaths, however, throughout the
14 entire range of these assumptions.

15 This graph explores how these results
16 depend on the assumption about the effect of
17 NSAIDs on mortality from GI bleeding. The
18 horizontal axis includes a range of possible
19 relative risks that measures the effect of GI
20 bleeding, and this range goes from a low on the
21 left of 1.0, which is no effect, to a high on the
22 right of a six-fold increase.

1 For this plot, all other effects of the
2 other drugs and the other outcomes were held
3 constant, so we could just look at the effect of
4 varying the relation between NSAIDs and GI bleed.

5 Note that even at the value of 1.0 on the
6 left, which corresponds to no effect whatsoever of
7 NSAIDs on mortality from GI bleed, there's still a
8 projected net increase of about 200 deaths. This
9 project increase is attributable entirely to the
10 effect of NSAIDs on acute renal failure.

11 And as you can see, as we increase the
12 assumed value of the effect of the relative risk
13 of NSAIDs on mortality from GI bleeding, the
14 projected number of deaths increases
15 substantially.

16 This slide repeats the projections that
17 you saw previously, but this time based upon
18 underlying or contributing cause of death. So
19 these risks, of course, are much greater, and the
20 projected number of deaths is correspondingly
21 greater. From these calculations, if 20 percent
22 of acetaminophen users switched to NSAIDs, these

1 calculations project an additional 3400 deaths
2 each year among U.S. adults. Even if only 1
3 percent of patients would switch from
4 acetaminophen to NSAIDs, the model estimates that
5 there would be an additional range of about 50 --
6 51 precisely -- to 250 people -- additional people
7 who would die each year as a result of that
8 switch.

9 So to summarize, these calculations show
10 that, under a broad range of assumptions, when
11 switching occurs, the risk of death increases.

12 The increased risk of death stems from
13 the fact that the population risks from acute GI
14 bleeding and acute renal failure are far greater
15 than the risk of acute liver failure.

16 Thank you very much.

17 DR. NELSON: Thank you very much.

18 Our next speaker is Dr. James Breitmeyer
19 from Cadence.

20 DR. BREITMEYER: Thank you. And thank
21 you, committee members, for the opportunity to
22 address you. I'm Jim Breitmeyer. I'm the chief

1 medical officer of Cadence Pharmaceuticals,
2 formerly of Eli Lilly and Harvard Medical School.
3 My colleague, Mike Royal, who has run the clinical
4 program for intravenous acetaminophen, is also
5 with me to answer questions.

6 Next slide, please.

7 We're present as an independent sponsor.
8 We've submitted an NDA for -- requesting approval
9 of a unique intravenous formulation of
10 acetaminophen in May of this year, with proposed
11 indications of acute pain and fever in adults and
12 pediatrics, with a proposed adult dose of 650 to
13 1,000 milligrams IV every four to six hours, up to
14 4,000 milligrams per day.

15 My primary reason for being here, while
16 the NDA is under review -- and this was with the
17 notification to the review division -- was that we
18 have some data that we think would assist the
19 committee with their deliberations, particularly
20 when it comes to pediatric dosing. And the
21 secondary reason is a request that, when
22 recommendations emerge from this process, that the

1 context in which acetaminophen is used by
2 considered with a consideration that controlled
3 usage in an inpatient environment is much less
4 likely to produce inadvertent overdose than
5 uncontrolled usage in an outpatient setting.

6 Next slide, please.

7 So I'm going to show you some liver
8 function data for hospitalized patients, and the
9 point of this is that, as you're considering the
10 likelihood that acetaminophen is involved in
11 causing liver injury in an individual, comorbid
12 disease is an important cofactor, and the data
13 show -- don't show a strong association between
14 existing comorbid disease in hospitalized patients
15 and additional liver injury caused by the use of
16 acetaminophen.

17 Then I'm going to present some newly
18 developed pediatric data and simulations which
19 suggest that the youngest patients -- and this
20 would apply particularly to children under two
21 years of age -- may be exposed to higher levels of
22 acetaminophen than we've all realized in the past,

1 and this may assist in developing dose
2 recommendation for the very young. And then,
3 finally, I'll summarize a hospital-based risk
4 minimization proposal that we've included in our
5 NDA.

6 Next slide, please.

7 We had an unusual source of data about
8 liver function tests in sick patients because of a
9 second produce under development at Cadence, which
10 ended development because of a lack of an efficacy
11 signal, but it had an excellent safety profile.
12 It's an antimicrobial peptide that's not
13 systemically absorbed, and showed no preclinical
14 hepatic toxicity. And so the LFT from our phase 3
15 trials offered an opportunity to look at
16 hospitalized patients without the confounding
17 factor of a potentially hepatotoxic study drug.

18 There were a total of almost 2500
19 patients who had baseline and post-baseline ALT
20 and bilirubin levels, and their concomitant
21 medication usage was known.

22 Because the studies were conducted in the

1 U.S. and Europe, we also had the opportunity to
2 examine any potential effect of receipt of
3 intravenous acetaminophen, approved in Europe as
4 Perfalgan, and prescribed in almost half of the
5 patients there as a 1,000-milligram IV regimen
6 every six hours.

7 Next slide, please.

8 And that was for period from 1 to 64 days
9 of having the regimen recorded as a concomitant
10 medication.

11 So the first point from the Omiganan
12 safety database is looking at all 2500 -- 2490
13 patients that -- almost 5 percent of them meet the
14 numerical criteria for Hy's law, 121 out of the
15 patient population, by having an ALT greater than
16 three times above normal limit, and a bilirubin
17 greater than 2X.

18 Now, a handful of these patients had
19 these central line in -- which was the entry
20 criteria to be in this study, so you can imagine
21 they're sicker than average hospital patients.
22 Now, a handful had a central line because they

1 were awaiting liver transplant, some of them for
2 acetaminophen-related overdose or toxicity. But
3 the vast majority of the patients in the upper
4 right quadrant were not receiving -- did not have
5 a medical history event or a concurrent medical
6 illness that was related to the use of
7 acetaminophen.

8 You can also see the Temple's corollary
9 quadrant in the lower right. 9.5 percent of this
10 hospital patient population fell in the range of
11 having a 3X ALT level.

12 So it's likely that many of these LFT
13 elevations have to do with the underlying medical
14 conditions of hospitalized patients. When we
15 examined the -- any effect of the use of oral
16 acetaminophen in the United States, the patients
17 that are in the upper right-hand corner were, in
18 fact -- oral acetaminophen was underrepresented.

19 Now, there is an obvious methodological
20 flaw to that, and that is if you're sick enough to
21 have a central line, then if you're taking oral
22 medication, you're less sick than your colleagues.

1 So that wasn't a very useful comparison.

2 But on the next slide, in Europe, we had
3 the opportunity to examine 700 patients who were
4 enrolled in these antimicrobial peptide trials.
5 And in this case, 2.1 percent of the patients who
6 received IV acetaminophen had a liver function
7 bilirubin and ALT result that would be considered
8 a Hy's law case, compared to 6 percent that had no
9 recorded concurrent acetaminophen dosage.

10 Now, of course, this is a retrospective
11 study. The major flaw would be that patients with
12 high LFTs wouldn't be prescribed acetaminophen.
13 And so, on the next slide, we have prospective
14 data which was derived from nine single and
15 repeat-dose studies of IV acetaminophen that are
16 contained in the Cadence NDA.

17 And what you can see is in this
18 hospitalized population -- probably a little less
19 sick than the one on the slide -- but in this
20 hospitalized population, with a
21 placebo-controlled, there are zero percent Hy's
22 law cases. And these are patients who received 4

1 grams a day in the repeated dose study, or 1,000
2 milligrams in the single dose studies. And this
3 was up to 48 hours of exposure. So we're
4 certainly not in the week, two-week, three-week
5 range that is of further interest to your
6 deliberations. But at least for shorter-term use
7 acutely in the hospital, there doesn't seem to be
8 any substantial drug-induced liver injury.

9 And in the Temple's corollary quadrant in
10 the lower right, in fact, the group receiving IV
11 acetaminophen was a little bit less likely to have
12 a 3X elevation of ALT than the group that received
13 IV acetaminophen.

14 So, moving on to our PK data on the next
15 slide, we have three studies that represent a
16 particularly rich data set for understanding the
17 pharmacokinetics of acetaminophen in the very
18 young. The first is a study conducted at the
19 Royal Children's Hospital in Australia by Greta
20 Palmer. Dr. Palmer gave us full access to the
21 study information. And we provided -- we
22 performed a meta-analysis of her data, in

1 combination with two Cadence pharmacokinetic
2 studies, one in neonates, infants, children and
3 adolescents, and one in adults.

4 The reason that the intravenous
5 acetaminophen data are relevant to your
6 deliberations is that acetaminophen is, by our
7 measurements, 93 percent orally available which,
8 accounting for first-pass metabolism in the liver,
9 suggests, as do animal data, that acetaminophen is
10 nearly completely absorbed in the GI tract.

11 So the PK parameters here should be, in
12 many cases, applicable to oral dosing regimens.

13 On the next slide, the data from all the
14 way from premature neonates through to the elderly
15 were evaluated in a pharmacokinetic modeling
16 exercise, and age and, in particular,
17 post-menstrual age, because of the large number of
18 newborns that are in this data set, was the factor
19 that was most significantly related to
20 acetaminophen clearance.

21 And what you can see is that the
22 clearance adjusted per 70 kilograms of body weight

1 is flat in this model in adults, adolescents and
2 children to the age of two, and then there was a
3 substantial fall-off in clearance below the age of
4 two. And, in particular, because of the large
5 number of patients provided by Dr. Palmer's study
6 from Australia, there is a substantial clearance
7 reduction in the very young, and this includes
8 quite a number of premature children as well as
9 full-term newborns.

10 And so on the next slide, the
11 implications of this for current dosing are shown.
12 We performed simulations and, in the box in the
13 upper right-hand corner, we have simulated areas
14 under the curve at 15, 12-1/2, 10 and 7.5
15 milligrams per kilogram, with the dotted line
16 toward the left at 51 microgram hours per
17 milliliter being the observed area under the curve
18 for an adolescent receiving 15 milligrams per
19 kilogram, which I think is a widely recognized
20 safe and effective dose for an adolescent.

21 And what you can see is that, in this
22 simulation, that neonates receiving 15 milligrams

1 per kilogram usually have an area under the
2 curve -- and this is the fifth dose -- usually
3 have an area under the curve that is substantially
4 larger than that observed in adolescents. And so
5 in this case we took the example of a
6 three-week-old neonate weighing 2.7 kilograms
7 receiving 40 milligrams, which is approximately 15
8 milligrams per kilogram.

9 So these simulations suggest that a 7.5
10 milligram per kilogram dose would be more suitable
11 in the neonate period. And as you go older from
12 neonates to two years, the simulated dosing and
13 recommendations that emerge from it converge, and
14 from the two years and above, the data don't
15 suggest that any changes in recommended pediatric
16 dosing should be considered.

17 On the next slide, our risk minimization
18 program is one that will be focused on the
19 hospital, and the hope here is that by performing
20 an intensive education and training program in the
21 hospital, that we will create behaviors and
22 information that will extend outside the hospital

1 and interact with the risk minimization efforts
2 that the -- that our colleagues in the OTC and
3 oral prescription world initiate.

4 And so the goal would be awareness of the
5 recommended maximum dose, which would be 4,000
6 milligrams a day, and avoiding excess acute dosing
7 in age groups, focused on hospital physicians,
8 nurses, pharmacists, and the patients themselves.
9 Dosing below -- in low body weight adults and
10 children will be PK-driven and lower than the
11 maximum doses that are recommended for full body
12 weight adults.

13 We will also be providing listings of all
14 acetaminophen-containing products and the amount
15 of acetaminophen that they contain for both
16 healthcare professionals and patients. And when a
17 patient leaves the hospital with a large bottle of
18 Vicodin, which happens often, we think it would be
19 very important for them to have a list of all of
20 the things that they have at home that also
21 contain acetaminophen.

22 We will also conduct an active monitoring

1 program, looking for any post-marketing evidence,
2 if the product is approved, of overdose, liver
3 toxicity and any related adverse drug reactions.

4 On the final slide, then, in conclusion,
5 perturbations in LFTs are common the hospital, and
6 acetaminophen administered intravenously at
7 recommended doses in a controlled setting does not
8 appear to cause liver injury above that of the
9 underlying diseases in hospitalized patients.

10 Our IV acetaminophen PK data for neonates
11 and infants shows an age-dependent decrease in
12 clearance below two years that suggests that
13 pediatric oral dosing guidelines might need to be
14 reconsidered.

15 And, finally, we will carry out an
16 educational program in the hospital to increase
17 awareness of appropriate dosing.

18 Thank you very much.

19 DR. NELSON: Thank you.

20 We've come to a point in time where we
21 are going to be able to ask some questions of the
22 sponsors prior to lunch. If anybody has any

1 questions.

2 Dr. Kramer?

3 DR. KRAMER: Judith Kramer. I have two
4 questions. First, for Dr. Rothman.

5 Dr. Rothman, it appears that the exercise
6 that you went through to understand that risk of
7 patients switching to NSAIDs was based on a
8 concern that McNeil, through Dr. Kuffner,
9 expressed that, if 650 were the maximum dose, that
10 patients would switch to NSAIDs. But I would just
11 like to ask you, I assume, but could you clarify,
12 that if, in fact, McNeil's recommended change to
13 recommend a 500-milligram initial dose led to
14 disappointment on the part of the patients such
15 that they, instead of going back to read the
16 package to see that they could take another
17 tablet, that they reached for their ibuprofen,
18 that the same implications would apply.

19 DR. ROTHMAN: Well, the calculations that
20 I presented were based on the assumption that
21 there would be a certain number of switching so --

22 DR. KRAMER: For any reason?

1 DR. ROTHMAN: For any reason.

2 DR. KRAMER: For any reason. And you are
3 not implying that there is empirical data to
4 suggest that if the maximum dose were 650 versus
5 1,000, that that behavior has been observed to
6 happen?

7 DR. ROTHMAN: That was not part of my
8 calculus.

9 DR. KRAMER: Thank you.

10 DR. NELSON: Dr. Cooper?

11 DR. COOPER: This question is for
12 Dr. Kuffner, regarding the pediatric dosing. In
13 the briefing materials, Dr. Kuffner, there was a
14 discussion regarding the -- two different
15 formulations, the infant drops and the children's
16 formulations. With the possibility that some of
17 the inadvertent dosing problems occurred with
18 parents giving the drops to children and providing
19 a greater amount.

20 In the root cause analysis that you
21 described, did you find that to be the case in any
22 of the therapeutic intent overdoses?

1 DR. KUFFNER: When you do go back and do
2 you the case level review of those specific cases,
3 you do find multiple different factors that are
4 involved. One of the factors, in the cases that
5 we reviewed -- in fact, 45 percent of the time, a
6 caregiver administered a volume of the infants'
7 concentrated product in teaspoons that we could
8 figure out, so they were not using the specific
9 dosing device that actually came with the product.
10 And that's one reason we feel that changing the
11 infants' formulation to have the PIBA that
12 includes the oral syringe, that that also has the
13 potential to decrease medication errors.

14 Also within the concentrated infants'
15 cases what you do find is confusion when a
16 healthcare provider actually gave recommendations.
17 And so in the specific cases they -- in some of
18 them they will outline that a parent or caregiver
19 was given information from a healthcare provider,
20 and assumed in those cases is that the healthcare
21 provider gave the dose to the parent or caregiver
22 in either a volumetric measure that was not

1 consistent with the dosing device, or specifically
2 gave the recommendation in teaspoons.

3 And that's one reason we feel educating
4 healthcare providers as well as educating patients
5 really is important.

6 We've actually done a fair amount of
7 education over the past number of years. And when
8 you go back and you look in our post-marketing
9 database what you find is we have not had a case
10 that occurred since 2004 with confusion with the
11 drops that led to moderate to severe or fatal
12 injury. And we do feel -- slide on, please --
13 that some of this is related to the efforts that
14 McNeil has focused in this area, to both alerting
15 healthcare providers as well as parents.

16 And here you see one of the execution of
17 that where we communicated this, and it went to
18 about 60 to 80 million consumers annually each
19 year, clearly calling out that the measure device
20 for your child's medicine is as important as the
21 medicine that goes in it, and also reinforcing the
22 message that our infants' medicine isn't half as

1 concentrated; it's three times more concentrated.

2 And we feel that these type of
3 educational efforts, which we are going to
4 continue to do in the future, have had an impact
5 and will continue to have an impact.

6 DR. NELSON: Dr. Day?

7 MS. DAY: This is for Dr. Kuffner also.
8 I was pleased to see McNeil's efforts for risk
9 evaluation and minimization strategies with a lot
10 of creative ideas and -- this is great. I do have
11 some concerns.

12 If we could see slide C-38.

13 I know that your icons and pictograms are
14 under development, and these are not the exact
15 ones. But I can illustrate with the one on the
16 right-hand side a question about how you would do
17 the comprehension testing.

18 So this one here, only 8 pills, and then
19 the max, 8 per day. The number 8 is very large,
20 and from my experience with comprehension testing,
21 I would not be surprised if there would be some
22 consumers who would take 8 pills every time. And

1 that would be not good, obviously.

2 So my question is, what plans do you have
3 for the testing, if you ask a direct question,
4 what is the maximum number per day -- that's one
5 kind of question. Have you developed plans around
6 scenario testing, where you give hypothetical
7 patients and what they do during a day, and then
8 ask appropriate questions of the participants?

9 DR. KUFFNER: So -- as you point out,
10 these are just examples. They are under
11 development. And we truly understand the
12 importance of making sure that we are
13 communicating the information appropriately. And
14 we're going to work with experts in the field.
15 We're going to test these. And Dr. Saul Shiffman
16 is here, one of the experts that we're working
17 with, to put this program together.

18 I don't know if you have a comment or two
19 on that.

20 DR. SHIFFMAN: Just in response to your
21 specific question, Dr. Day, this would be tested
22 with scenario testing; that is, where -- just to

1 explain to everyone, scenario testing is where,
2 instead of asking a direct question, which makes
3 it kind of an open book test, you present a
4 consumer or a respondent with a scenario. You
5 know, Mary has a headache. She wants to take this
6 medication. How much should she take? So that
7 you're really asking the person to solve the kind
8 of problem that they need to solve in actually
9 using the medication.

10 And as you've heard from Dr. Kuffner, the
11 idea is that these would need to be tested -- and
12 we have brainstormed other ideas, like having the
13 8 arrayed around the clock, precisely in order to
14 make clear that the 8 is the maximum, but has to
15 be arrayed over the day.

16 In the end, it doesn't matter how much --
17 what we think of it, but rather, as you've said,
18 how consumers respond to it.

19 MS. DAY: That sounds great. I just --
20 final comment, and that is, in scenario testing,
21 you're still asking a free report. You're saying,
22 Mary has a headache, blah, blah, blah. How many

1 should she take. As opposed to, here's Mary and
2 Sam and Joe and someone, and give them specific
3 things that they do during the day, and ask if
4 they're okay or not. Then you can systematically
5 test different conditions.

6 DR. SHIFFMAN: Agreed.

7 DR. NELSON: I think I inadvertently cut
8 Dr. Kramer off before, so she's got a second
9 question.

10 DR. KRAMER: I had a question for
11 Dr. Kuffner. In your root cause analysis, you
12 identified that one of the issues was inadvertent
13 overdose using multiple APAP-containing
14 medications. And yet McNeil disagrees with the
15 FDA recommendation to eliminate combination
16 products.

17 And of the suggestions that you gave in
18 your presentation, it appeared the only thing that
19 addressed that was the proposed icons.

20 And yet I could imagine that if you --
21 for instance, the one with the maximum dose, even
22 if you made clear that that was the maximum daily

1 dose of one medication, that would almost set you
2 up to say, it's okay to take eight of this, and if
3 they have another medication they're taking, it's
4 okay to take six of this. You would still have
5 the problem of multiple medications containing
6 acetaminophen.

7 Could you explain, beyond the icons, what
8 you're recommending to deal with inadvertent dose
9 of multiple -- of acetaminophen contained in
10 multiple combination medications.

11 DR. KUFFNER: Sure. So McNeil's risk
12 mitigation framework is based upon changes to
13 packaging, changes to labeling, as well as
14 enhanced education. And so icons and pictograms
15 are one way to communicate information on the
16 package at the point of use.

17 What we're also putting together is an
18 enhanced education effort. And as I said earlier,
19 we have been educating over the past number of
20 years. We do feel as though this multi-faceted
21 approach really will be effective. Packaging has
22 been demonstrated to be effective, especially

1 around child-resistant packaging and labeling.
2 When it comes to the Reye's syndrome warning --
3 certainly did change patient and consumer
4 behavior. So we feel changes on the label will be
5 effective.

6 And when it comes to education, we have
7 been educating over the past number of years, and
8 we actually have seen a decrease in the number of
9 people taking more than the recommended dose, as
10 well as people taking -- using multiple
11 acetaminophen-containing medicines at the same
12 time. And that data actually comes from the Slone
13 survey where they -- it's a population-based
14 telephone survey where they go out and determine,
15 are people taking multiple medicines at the same
16 time? And we have actually seen a decrease in
17 that survey during the time period that we started
18 educating patients.

19 DR. NELSON: Dr. Griffin?

20 DR. GRIFFIN: Yeah. Marie Griffin. This
21 is a question for Dr. Cathy Gelotte. In all
22 except one of the examples that you gave in the

1 studies where the 1,000-milligram dose seemed
2 superior were examples of surgical interventions.
3 In my experience, patients usually get
4 prescription drugs or acetaminophen combinations,
5 not acetaminophen alone.

6 So how often is this -- acetaminophen
7 alone given for these types of surgical
8 procedures? And is that really relevant to most
9 acetaminophen use?

10 DR. GELOTTE: I'll begin by saying, in
11 clinical development of analgesics, we have to
12 develop certain types of models, and FDA has
13 accepted the dental pain model as a model that's
14 sensitive enough of enough severe pain to
15 distinguish between doses and also to distinguish
16 between analgesics.

17 So there are other models that
18 acetaminophen has been tested in, tension
19 headache, dysmenorrhea, the types of pain
20 conditions that you would see over the counter,
21 but they are of lower level in severity of pain in
22 order to be able to distinguish, what would that

1 incremental benefit be by dose.

2 So you're right, we use models in drug
3 development, and this is a reasonably accepted
4 model to be able to distinguish that incremental
5 benefit.

6 DR. NELSON: Just so the panel knows,
7 we're actually keeping a list, so once you raised
8 your hand -- hopefully we've written your name
9 down. The next person on the list is Dr. Lorenz.

10 DR. LORENZ: Just a follow-up question to
11 that because, with regard to the non-inflammatory
12 pain models, I guess in thinking about the
13 implications of these dose differences for
14 patients with osteoarthritis, even if pain tends
15 to be lower, are you suggesting that, in
16 non-inflammatory models, the difference that you
17 illustrated in the dental pain model would not be
18 observed?

19 DR. GELOTTE: I'm sorry. I didn't hear
20 the beginning part of your question. Please --

21 DR. LORENZ: Given that non-inflammatory
22 models are ones that are, in fact, perhaps more

1 relevant to the osteoarthritis or chronic pain
2 that drives these different dosings in many pain
3 situations, are you implying, then, that the
4 difference that was illustrated in the dental pain
5 model is not characteristic of these dosing
6 studies in non-inflammatory pain?

7 DR. GELOTTE: In terms of
8 non-inflammatory pain, I think in the
9 osteoarthritis trial that we showed, that's the
10 only one that we had two doses, two dose levels.

11 In general, the effect size for
12 acetaminophen -- it is for mild to moderate pain.
13 It's about 24 percent. And they're used in terms
14 of WOMAC scales and more quality of life in
15 patient global. So that's where you see that type
16 of pain. So I'm not sure if I'm getting your
17 question directly.

18 DR. LORENZ: I'm really asking if there
19 are any studies other than the dental pain model
20 that illustrate this difference between the 1,000,
21 650 and 500 milligrams --

22 DR. GELOTTE: In the multiple dose --

1 DR. LORENZ: -- that support the
2 contention that a 1,000-milligram dose is needed
3 versus -- it was actually versus -- I'm sorry --
4 versus ibuprofen, I think, right?

5 DR. GELOTTE: Oh, ibuprofen.

6 DR. LORENZ: Sorry.

7 DR. GELOTTE: Okay. What you saw today
8 in terms of the comparison with the 650 versus the
9 400, those were all of the studies that we found.
10 So the two that were published and the three that
11 were unpublished.

12 DR. LORENZ: And my other question for
13 you -- I think you showed a slide where you looked
14 at different total daily doses of acetaminophen,
15 and you used a 2-gram dose and a 4-gram dose. But
16 I wondered if there's any information on the daily
17 dose in the midpoint of that, which might be more
18 relevant to some of the unit doses that are being
19 considered?

20 DR. GELOTTE: No, I'm not aware of any.

21 DR. LORENZ: Thank you.

22 DR. NELSON: Dr. Heckbert?

1 DR. HECKBERT: Yes. Susan Heckbert. I
2 have a question for Dr. Rothman. It relates to
3 the calculations you did that showed somewhere on
4 the order of 200, 300, 600 additional deaths if
5 people switched -- if 5 percent to 20 percent of
6 people switched from acetaminophen to ibuprofen,
7 or to NSAIDs. That's per year, is it?

8 DR. ROTHMAN: Those are deaths per year,
9 yes.

10 DR. HECKBERT: Per year. So I was having
11 trouble squaring those numbers, which seem large,
12 with the AERS counts of death from all adverse
13 effects for select analgesics by year that was
14 part of our briefing materials. And I know the
15 AERS is an underestimate of a lot of things, but
16 maybe death is less problematic than other
17 end points. But for acetaminophen, it's
18 consistently considerably higher than for
19 ibuprofen and some other analgesics. It's way
20 lower in terms of deaths. And I'm just having
21 trouble reconciling these two -- your estimates
22 with the death report information.

1 Can you explain to me how you could get
2 hundreds more deaths if only 20 percent of people
3 switch when you don't see that in the AERS data
4 for current --

5 DR. ROTHMAN: Well, the AERS data --
6 you're referring to the self-reported database of
7 adverse events so --

8 DR. HECKBERT: Yes.

9 DR. ROTHMAN: In the AERS data, the -- I
10 think the problem is that the more common the
11 disease, the less likely it is to be reported.
12 Wouldn't that be an issue for the AERS data?
13 These deaths that we're projecting come from the
14 actual total risk of death calculated from vital
15 statistics, coupled with the relative risks from
16 reported epidemiologic studies. And so they're
17 not derived from self-reports.

18 DR. HECKBERT: Right. I guess I'm
19 having -- I don't see any reason that the deaths
20 reported with acetaminophen should systematically
21 differ from the deaths reported with ibuprofen in
22 the AERS data, because they're both drugs that

1 have been around for a long time and are
2 well-accepted. So I --

3 DR. ROTHMAN: But they'd be reported for
4 different outcomes. My point was that the
5 outcomes that are reported in relation to
6 ibuprofen might be less likely to prompt reporting
7 than the -- ordinarily, you would expect that the
8 strongest associations would lead to a report and
9 the weaker associations would not.

10 The weaker associations, in this case,
11 though, are associations for NSAIDs that relate to
12 more common problems and, therefore, they will
13 have a larger attributable number of deaths, even
14 though the strength of the association is weaker.

15 So the 10 to 200-fold increase in liver
16 failure events is very strong, but affects fewer
17 people than the more modest associations for GI
18 bleeding and for acute renal failure, which are
19 affecting larger numbers of people.

20 DR. NELSON: Dr. Wolfe?

21 DR. WOLFE: There's obviously a
22 bubbling-over disagreement between the FDA's

1 suggestion that the over-the-counter combination
2 products be removed, and the attitude by the
3 company -- companies. In some materials that the
4 FDA presented for the meeting now seven years ago,
5 they estimated that about a quarter of the
6 fatalities in the AERS database having to do with
7 acetaminophen were from combination products, and
8 the -- probably an important genesis of the
9 suggestion that combination products
10 over-the-counter be removed was that it is easier
11 for someone to confuse combination products as in
12 not focusing on the acetaminophen than just pure
13 acetaminophen.

14 So my question is that in the data that
15 we were presented this morning by Dr. Lewis -- and
16 I think it's consistent with other data -- a very
17 small percentage of the test fatalities for
18 example are with combination products, and much
19 larger than with the single ingredients.

20 It seems unlikely, given that so many of
21 the deaths in the AERS database are more than one
22 product being used, more than one combination

1 product -- what happens if someone is taking a
2 single-ingredient acetaminophen product and a
3 combination one? How did that get counted?
4 Because there isn't any category of this in the
5 test data, and I just don't -- I don't know the
6 answer to it.

7 It would seem, though, that there would
8 statistically be a fair number of people who were
9 taking one from the single-ingredient category and
10 one from the multiple-ingredient category, and if
11 that were so, where do they show up on these data?
12 There isn't any such category as that.

13 And that's an important issue because if
14 you're -- the logic of doing something about the
15 combination products is that it is confusing to
16 people. They don't know -- Dr. Kramer raised a
17 question about this, too. People are less likely
18 to know that something is acetaminophen if they
19 have one or two or three ingredients in it. So I
20 just -- my question is to anyone on the industry
21 side, or the FDA side -- maybe that can be a
22 question this afternoon -- what happened to those

1 people that died who were taking more than one
2 acetaminophen-containing product and one was a
3 single-ingredient and one was a
4 multiple-ingredient? How did that get counted?

5 DR. DART: Rick Dart. I'm the
6 president-elect of AAPCC, and several of the
7 people around the table are familiar with AAPCC
8 data. The way they're counted is we're based on
9 mentions, so it's counted both ways.

10 So if you have a single-ingredient, you
11 count as a single-ingredient, and if you have a
12 combination, you count as a combination. And if
13 you have both, you count twice in the database.

14 Now, in the last couple of years, we have
15 started to break --

16 DR. WOLFE: The AERS database also or
17 you're just talking about --

18 DR. DART: No. I'm just talking about
19 what we call NPDS now.

20 DR. NELSON: Just -- as predicted, with a
21 panel of 45 people, we're going to have some
22 trouble running into lunch, and maybe -- we have

1 enough people on the list at this point to last us
2 through the end of the day if we just keep going
3 down.

4 So what I'd like to really do is take one
5 final question before we take a break for lunch,
6 if that's okay. And then obviously all the
7 questions will be able to be answered, hopefully,
8 during the remainder of the sessions during the
9 day. But if we can get this last question from
10 Dr. Walker-Harding, and then we could take our
11 break.

12 DR. WALKER-HARDING: This question is for
13 any McNeil or any of the other industry -- the
14 oral administration of acetaminophen. I had a
15 question about the adolescent population. I saw
16 data that looked at 12 and under, five and under
17 and adult, and I'm concerned that I didn't see 12
18 to 18-year-old age group and how they are
19 specifically going to be addressed in education
20 and how their metabolism works with acetaminophen.

21 The one study from -- Dr. James
22 mentioned, they had 157 kids they looked at that

1 needed treatment for acetaminophen intoxication,
2 and they -- 83 percent of those kids were
3 adolescents. And even for intentional and
4 unintentional ingestion, they're different from
5 pediatrics because they can acquire and use it
6 without their parents administering it, but yet
7 they're not adults and may not have the
8 understanding of the kind of labeling you are
9 putting on the box.

10 So I was wondering, how are you
11 addressing adolescents specifically?

12 DR. KUFFNER: So within our analysis, the
13 root cause analysis, we categorize them in the 12
14 and above age group, but you do bring up a good
15 point. It's extremely important to educate not
16 just adults and not just caregivers, but
17 adolescents. And as we put forward this plan to
18 encourage people to always use the lowest
19 effective dose, we feel it's critically important
20 to actually get to adolescents before they develop
21 their medicating behaviors.

22 And so part of our broad-based education

1 campaign will be targeted, at least part of it,
2 towards adolescents to encourage that they always
3 take the recommended dose; don't take multiple
4 medicines that contain acetaminophen. And we feel
5 the opportunity really is targeting people who
6 have developed the medicating behaviors, but a
7 real opportunity before they develop medicating
8 behaviors that aren't consistent with the package
9 labeling.

10 DR. NELSON: Okay. Thank you, and thank
11 everybody for understanding. Before we break for
12 lunch, two items.

13 One, the committee is again reminded to
14 refrain from discussing this meeting topic during
15 lunch or during the breaks.

16 Secondly, Dr. Ganley has provided with us
17 a complete pharmacopeia of any -- or many
18 over-the-counter acetaminophen preparations right
19 up here. And anybody on the committee that would
20 like to come look at the boxes and see what's
21 included in the label, please feel free to walk up
22 and take a look.

1 MS. FERGUSON: And for the committee
2 members, just to let you know that your -- the
3 people at the table, if you'll head out these
4 doors to the right, then you have to take a second
5 right, and it will be on your left-hand side.
6 It's across the hall from the main kind of buffet
7 cafeteria area.

8 DR. NELSON: And we will reconvene in one
9 hour, at 1:15.

10 (Whereupon, at 12:15 p.m., a luncheon
11 recess was taken.)
12
13
14
15
16
17
18
19
20
21
22

1 AFTERNOON SESSION

2 (1:19 p.m.)

3 DR. NELSON: Welcome back, everybody.

4 Our first guest speaker for the afternoon is
5 Dr. William Lee, the Meredith Mosle chair in liver
6 diseases at UT Southwestern Medical Center in
7 Dallas to speak about the acute liver failure
8 study group.

9 DR. LEE: Thank you very much,
10 Mr. Chairman. It's my task to go over the
11 association that we've made within the acute liver
12 failure study group with acetaminophen, and I
13 might say that I'm happy to be back for my second
14 appearance here. I spoke on the same data seven
15 years ago, in 2002. And three years later we
16 published the so-called Larson paper that you have
17 referred to, and has been referred to already.
18 And I'm happy to say that Ann Larson, who at that
19 time was at UW in Seattle, has moved southward and
20 eastward to Dallas and is now our head of
21 transplant hepatology at UT Southwestern.

22 So what I'm going to do today is review

1 some of the background of the relationship between
2 acute liver failure and acetaminophen clinically
3 as we know it, go over a little bit of the Larson
4 data, and then -- she's been good enough to help
5 me update that data to a new data set of 606
6 patients that represent the current standing, or
7 up until very recently, of our database.

8 So just to review, acute liver failure is
9 the most severe form of liver injury we know. In
10 the pre-transplant era, less than 10 percent of
11 the people survived. It's classified in the UNOS
12 system as status 1, the most urgent, for requiring
13 transplantation, and it has a lot of interesting
14 and frustrating features and has been difficult to
15 study.

16 What's interesting about it, from one
17 standpoint, is that with all these different
18 etiologies, including of course acetaminophen,
19 they all funnel down to a very common clinical
20 pattern with the features of coma, coagulopathy,
21 that are the hallmark features, but also
22 vasodilatation shock, bleeding is frequent,

1 infection is frequent and, as I'll show you later,
2 renal failure as well. So it's a remarkably
3 consistent syndrome across a variety of
4 etiologies.

5 It's the most common -- now, APAP itself
6 causing acute liver failure is the most common
7 form of ALF in the western world, 70 percent in
8 Denmark, 60 percent in the UK, 46 percent in the
9 U.S.

10 It outweighs all other idiosyncratic drug
11 reactions by three-fold. The number of deaths in
12 the U.S. annually, according to our data is about
13 double, but the number of cases of ALF is 46
14 percent versus about 12 percent for all other
15 idiosyncratic drug reactions leading to liver
16 failure.

17 On the other hand, it's been considered
18 safe, and I would contend that that's probably not
19 a good claim.

20 Unintentional cases do slightly exceed
21 the suicidal cases in ALF, but there's a whole
22 bottom of the iceberg, below the water line, if

1 you will, of cases that are hospitalized, as I'll
2 show you in a moment, but don't reach this stage
3 of liver failure. And there's a complexity to all
4 the liver failure cases, I would say in that, as
5 you've heard, narcotic use is prevalent, alcohol
6 use, and also illicit drugs. And it's these
7 complex cases that really are the ones that most
8 frequently get to liver failure.

9 This is a coupon that I got several years
10 ago when I was buying my -- renewing my statin
11 prescription, and I don't think McNeil had it in
12 for me, but it does say here "safest."

13 Now, there's a hierarchy, as I said a
14 moment ago, of the severe cases up here that meet
15 the criteria for acute liver failure with an INR
16 of 1.5 and any degree of encephalopathy. There's
17 another group that we've defined recently -- and
18 it's arbitrary on our part, I guess, as acute
19 liver injury, those that have significant INR
20 prolongation, but no encephalopathy, and we're now
21 chronicling these cases in the ALF study group.

22 There's another group that are

1 hospitalized with elevated aminotransferases --
2 and again, this is an arbitrary value, but let's
3 say, if your normal -- upper limit of normal is
4 40, this would be an ALT of around 800. And then
5 there's a group that gets hospitalized and has no
6 ALT elevation, but they do receive NAC, and so
7 they certainly have a two- or three-day
8 hospitalization to get the NAC treatment.

9 Now, before the ALFSG started, we had
10 done this study had Parkland Hospital, which was
11 published in 1997, which does take into account
12 all comers. There's a little glitch down here.
13 This should be 13 percent here, and 87 percent
14 here. It's a PC Mac thing.

15 But if you looked at all the comers over
16 a three-year period -- it was a retrospective
17 study in this large Dallas County Hospital,
18 Parkland -- we saw and divided them into those
19 that could clearly be identified as suicidal,
20 suicide admitted single time point, no cause for
21 pain, versus what had been called therapeutic
22 adventures by Zimmerman and Seeff, and later by

1 Maddrey and Seeff. We call them unintentional and
2 pointed out that suicide was denied, that they
3 were taking the medication over several days, and
4 that there was typically a very clear reason for
5 pain.

6 What we noted, however, was that this
7 group came in at a median of four hours after the
8 ingestion -- some later, but most within this time
9 frame -- whereas this group, not knowing that
10 anything had happened to them, came in late,
11 usually 36 to 48 or even 72 hours after their last
12 ingestion, but they had been ingesting for several
13 days.

14 This group -- only 20 percent had
15 elevated aminotransferases and only one out of 50
16 died, whereas virtually all of these patients had
17 ALT elevations, and there were eight deaths.

18 So if you add up 9 divided by 71, you get
19 13 percent, the top of the iceberg, and there's at
20 least 87 percent down here of cases that don't
21 reach the criteria of ALF. So what I've said over
22 here -- and it's a little bit off the slide to the

1 left, at least in my view -- is that the
2 difference between the Parkland study that takes
3 in all cases versus the acute liver failure study
4 group is that we are now going to focus for the
5 next six or eight slides on just the top of the
6 iceberg here.

7 So ALF is believed to involve perhaps
8 2,000 cases annually. Each hospital has one to
9 five to ten to 20 cases perhaps. There is no
10 viable treatment for all patients, unless you
11 suggest that N-acetylcysteine is the treatment --
12 and we do have a manuscript that's in ePub to
13 Gastro right now -- that's out in ePub, saying
14 that NAC works in non-acetaminophen cases.

15 But, again, the background of this is
16 that Hep B was the predominant form prior to 1980,
17 and even in the early '80s and mid-'80s and the
18 '90s, it was about 20 percent of the ALF cases
19 were due to acetaminophen.

20 So we began the network 11 years ago, in
21 1998, to study this rare condition, and over the
22 years we've enrolled roughly 150 cases a year, to

1 the current number of 1400. 23 sites participate.
2 We've gotten out a lot of original manuscripts.
3 We've completed the clinical trial of NAC. It was
4 a positive trial for early phase hepatic failure.
5 And we've standardized the protocol that we use
6 across all sites, and you heard this morning
7 Dr. James' review of the adducts assay which was
8 generated in part from our group.

9 We've also conducted all kinds of other
10 ancillary studies of cytokines, measuring
11 troponins, measuring -- studying the molecular
12 virology of Hepatitis A in this setting, and
13 Hepatitis B.

14 This is what our case report form looks
15 like. The first -- that's the upper half of the
16 first page. We have an admission form and then a
17 ten-page CRF. We collect serum, plasma, urine.
18 It's prospective. We get our outcomes at three
19 weeks, and then have a long-term follow-up visit
20 at one and two years.

21 This is the spectrum of etiologies across
22 the adult registry for 1321 cases -- the latter

1 half of 2008 was when this closed out -- 46
2 percent due to acetaminophen, 12 percent due to
3 idiosyncratic drugs, 7 percent due to Hepatitis B,
4 3 percent due to Hepatitis A -- and these are both
5 declining -- and 15 percent are what we call
6 indeterminate, meaning the PI, the site PI who was
7 closely involved in the patient's care, could not
8 determine what the cause was after appropriate
9 serologic testing and history-taking.

10 This is the number of acetaminophen cases
11 as a percent of all the ALF for that year. So it
12 looked like it increased through 2003-2004, and
13 perhaps has been slightly decreasing over the last
14 few years.

15 Now, this is a slide from the Larson
16 paper that I referred to. She looked at 275
17 cases. 253 clearly had intentional or
18 unintentional -- and you see almost even numbers
19 here. And the characteristics of the cases are
20 that they were largely women, that the dose was
21 roughly 25 grams at a single time point in this
22 book, and nearly that in the unintentional cases,

1 but it was averaged to 7.5 per day, which
2 suggested that perhaps they were taking it on
3 average for three days.

4 The coma grade of those who were greater
5 than grade 3 -- that is, grade 3 or grade 4 -- on
6 admission was higher in the unintentional; we
7 think that's probably due to the higher use of
8 narcotics in that group because they weren't worse
9 in terms of severity in terms of their overall
10 outcome, with 66 and 64 percent spontaneous
11 survival; that is, without transplantation.

12 As you might think the ALT levels are
13 lower slightly, but still towering values in the
14 unintentional group. And, again, the history of
15 depression was more common in the suicides, but
16 the narcotic use was common in the patients going
17 for pain relief -- as well as the use of multiple
18 preps.

19 Now, that's the data up until the end of
20 2003. Now I'm going to begin giving you some
21 additional new data. And I will preface it by
22 saying that this is work that Ann and I did in the

1 past three weeks in preparation for this meeting.
2 It's not a manuscript, and it's not final, and
3 there may be one or two mistakes in it, perhaps
4 more.

5 So -- this is messed up a little bit
6 again by the Mac PC thing, but with that apology,
7 you see that the cases now -- we have 606, a
8 little bit more in the unintentional group
9 perhaps. Still mostly women. Age is slightly
10 older in the unintentional group.

11 Acetaminophen looks higher -- and we've
12 got to look at that again. We think we're getting
13 more careful information. It's 38 grams -- but
14 that's a lot. 47 here, but divided to be roughly
15 the 7-gram level that we mentioned before.

16 Many of these people, as I've said before
17 at other settings, are taking Vicodin, let's say,
18 at 8 or 10 or 12 per day for several months, and
19 then get an acute hit. But you see it's still a
20 very acute hit. We don't recognize any chronic
21 injury scenario that I am aware of.

22 The ALTs are high. The slight increase

1 in coma grade on admission. Alcohol abuse was
2 present in 50 percent of both groups -- sorry --
3 use 50 percent, abuse 18 and 17 percent.
4 Antidepressants, roughly the same.

5 But this is a new part that I've
6 highlighted here -- and, again, I apologize for
7 these slides not coming out nice and crisply. So
8 we separated them out in this analysis for use
9 only over the counterpreparation, 49 percent for
10 the intentional, 32 percent for the unintentional.

11 Narcotic compound, roughly even at about
12 40 percent. And acetaminophen plus the narcotic
13 acetaminophen compound -- am I making that clear?
14 This is the APAP plus hydrocodone or whatever.

15 So in the pain relief group, in the
16 unintentional group, 27 additional percent were
17 taking APAP plus Vicodin or Lorcet or whatever.
18 So that gives you a total taking the narcotic in
19 the unintentional group of 68 percent versus 50
20 percent over here. Again, the survivals are
21 relatively similar.

22 Now, here's a comparison for the 606

1 between -- if you separate them male and female.
2 Again, the ages are similar. The males have a
3 slightly higher percentage of suicides, more
4 alcohol, less antidepressants -- again, more using
5 OTC by itself. Still a fairly significant number
6 using multiple preps and using narcotics. Again,
7 coma grade a little bit higher in the women,
8 presumably because there's more narcotic use over
9 here.

10 Again, if you look at the early stage,
11 '98 to 2003, versus 2004 to 2009 -- let's just
12 compare them and see if there's any significant
13 differences. There are a couple. The percent
14 suicide seems to be going down a little bit, more
15 unintentional cases. The percent with alcohol
16 use -- perhaps a difference; not much.
17 Antidepressant use -- I'm not sure about this
18 number. That's the one I would worry about
19 because I thought it was 37 or 38 in the first
20 period before.

21 Psych illness seems to be more prevalent
22 now. Drug abuse history seems to be more

1 prevalent now. Are we getting better histories?
2 I'm not sure about that. And, again, if you look
3 at only one OTC product, it looks like it's now 20
4 percent versus 54 percent before. And, again, the
5 narcotic -- or narcotic plus plain APAP groups are
6 higher than they were previously.

7 What were the reasons that these people
8 were using it for pain? And I haven't shown every
9 single category here, but chronic pain, not
10 otherwise specified -- again, early and late --
11 roughly the same. All of these are roughly the
12 same, but I played this out since I don't think
13 we've shown this before; it's not in the Larson
14 paper. Back pain was a very common theme.
15 Abdominal pain, headache or migraine. Viral
16 illness is still about 5 or 10 percent of the
17 cases -- and again, we put this down for
18 completeness sake. And I'm not sure why there's a
19 higher number of so-called unknown reasons down
20 here, except that perhaps we're being more careful
21 about the history-taking.

22 So the overall message, from this update

1 of the Larson paper, I would say, is that the
2 overall pattern is similar between the early
3 period and the later period. There seem to be
4 slightly more unintentional cases, perhaps
5 slightly better outcomes, and overall -- perhaps a
6 decrease in the overall percent of our ALF
7 registry cases.

8 In this ALI group that I mentioned, we've
9 now enrolled, over the past 15 months, about 40
10 cases of ALI. 71 percent of them -- again, IRN 2,
11 no encephalopathy. 71 percent of them were APAP.
12 We're seeing plenty of cases who don't make the
13 ALF registry, but we still are enrolling them to
14 gather their data.

15 About 40 percent of the suicidal or
16 unintentional cases were taking a narcotic-APAP
17 compound. More unintentional cases used
18 additional APAP. And there looks like there's an
19 increase in the use of the narcotic compounds in
20 the recent time period. But I say this is -- this
21 is not mature data, if I can say it that way.

22 So, in summary, nearly 50 percent of all

1 ALF is acetaminophen. It's mostly women. There's
2 some alcohol use and abuse involved, slightly more
3 unintentional. There's no seasonal pattern to
4 this. It's just about 25 percent in each quarter.
5 And the overall survival remains good because
6 there is spontaneous survival in about two-thirds,
7 about 8 percent getting transplanted. But still
8 there's 26 percent that either die or get
9 transplanted, and it's still the largest group of
10 the ALF patients.

11 So -- I would be neglectful if I didn't
12 put in some pediatric ALF data, and I am grateful
13 to Rob Squires for providing me with this data.
14 FDA would like to have put him in, but the
15 schedule obviously is very tight. He will,
16 actually, be here tomorrow if you have questions.

17 The PALF started a couple of years after
18 us. It actually started when Rob was in Dallas,
19 and now he's at the University of Pittsburgh.
20 They have over 800 cases enrolled. They,
21 interestingly enough, have three sites out of the
22 U.S. They have a similar registry to our registry

1 in terms of collecting seven-day data and bio
2 samples, and they have an ongoing trial of NAC
3 right now.

4 Here are the sites involved. They are
5 outstanding pediatric investigators at the 20
6 sites -- and, again, it's an NIDDK-sponsored
7 study, as is mine.

8 And here's the data divided up between
9 those under one year of age and those over one
10 year of age. And I've highlighted, for your
11 purposes, the APAP cases. The huge number of
12 cases in the under one year of age group are
13 largely metabolic or indeterminate. You see
14 there's a total of 93 out of -- there's close to
15 250 cases in the under one year old group in terms
16 of their overall group is 808. But there are
17 precious few acetaminophen cases in this age
18 group.

19 When you get to older children, there are
20 some showing up in the one to five and six to ten
21 group. I'll comment on these in a moment. But
22 the vast majority, 85 out of 108, are adolescent

1 girls taking overdoses, impulsively, presumably,
2 in a suicide attempt.

3 So here's their summary. There's 103
4 cases of APAP out of 808. There's a small number
5 that are thought to be chronic exposures, but the
6 group is now looking -- and I hope Rob will be
7 able to speak to this tomorrow because I didn't
8 feel comfortable sharing that data. They have
9 roughly 50 patients that they feel have had
10 chronic exposures. Some are not considered
11 primary APAP, but where there's been chronic
12 historical evidence for overexposure to APAP.

13 Basically, the caregivers failed to
14 realize they were giving too much drugs, so they
15 fit into an unintentional kind of group; they're
16 calling them chronic exposures. And these people
17 were typically under ten years of age, had normal
18 APAP on admission, worse encephalopathy on
19 admission, but relatively similar outcomes.

20 In the overall PALF group, about 5 -- due
21 to APAP, about 5 percent die and 5 percent are
22 transplanted. And, again, among those greater

1 than age ten, the most common cause of ALF is an
2 overdose of -- typically in a young girl.

3 So -- just a little bit more granularity
4 to this issue. This is a very quick look at some
5 of our data to show you the way that acetaminophen
6 cases contrast with the drug-induced liver injury
7 cases. Acetaminophen, you should understand, is a
8 hyper-acute injury. It's maximal within 72 to 80
9 or so hours after a single time point ingestion.
10 The number of days from jaundice to coma is
11 essentially zero, versus a sort of sub-acute
12 presentation in the DILI group. They resemble
13 each other in certain ways, but they differ highly
14 in the ALT values and in the bilirubin values and
15 in the outcomes because the DILI cases rarely get
16 better; only a quarter survive without a
17 transplant, and nearly one-half get transplanted.

18 You've seen this slide before from
19 Laura -- or a similar one -- and this is just to
20 say that I'm going to talk about adducts for
21 another minute -- and Laura's presentation was
22 good in that regard. This is the slide that she

1 showed you before, showing the known APAP versus
2 the small group of 18 percent of the indeterminate
3 cases out of 36 patients that we published in
4 2006.

5 Now what we're doing here -- and, again,
6 this is data you have not seen -- we are combining
7 and performing the adduct assay on a larger group
8 of indeterminates, 158, and going back to the
9 Larson sera for what was originally 275 cases in
10 the 2005 hepatology paper.

11 We had serum samples on an aggregate of
12 309 of these cases. If you divide them up into
13 the 199 Larson cases, and perform the adduct assay
14 with the improved assay Dr. James mentioned, 188
15 out of that 199 were strongly adduct-positive; 11
16 were adduct-negative -- and I'll talk about those
17 in a moment.

18 In the indeterminate group -- again, a
19 much larger sample size, 110 -- we had 20 that
20 were adduct-positive -- and, again, they're in the
21 same highly toxic range -- and 90 who were
22 assay-negative.

1 This is 18 percent, once again, as it was
2 in the previous paper.

3 When you look at the assay-negative group
4 here, these people -- most of them had presented
5 late. They were five, seven, 12, 14 days after
6 the ingestion, so ostensibly their
7 aminotransferases were lower and their adduct
8 assay still probably had been positive earlier
9 on -- that's an assumption on my part, obviously.
10 But we retested second serum samples on these
11 patients, and they were still negative.

12 For the assay-positive group, many of
13 these people -- 14 out of 20 -- had a history of
14 some acetaminophen use. But the site investigator
15 presumably was uncertain about calling it
16 acetaminophen because either there were other
17 mitigating possibilities, or that the patient was
18 in coma grade 3 -- something like 12 out of 20
19 were in coma grade 3 on arrival to his hospital.

20 So if you look at the adduct group -- and
21 I won't dwell on this slide, but if you look at
22 them, the profile of the known acetaminophen group

1 resembles almost identically -- and Laura touched
2 on this -- the adduct-positive indeterminate
3 patients, with very high aminotransferases, high
4 adduct levels, low bilirubins, that hyper-acute
5 presentation picture. But notice that while this
6 group, known to have acetaminophen poisoning,
7 received NAC, only 40 percent of this group had
8 received NAC. And, once again, the
9 adduct-negative truly indeterminate group had low
10 aminotransferases, no adducts, high bilirubins, as
11 you would expect, and again, even less NAC use.

12 This is what it looks like for the ALT
13 levels. Almost everyone in both groups of these
14 known APAP cases had aminotransferase levels above
15 1,000 -- a few below, not many -- and almost all
16 except the 11 that we mentioned had adduct levels
17 that were sky high.

18 Now, Dr. James also touched on the
19 complexity of the toxicity, what cytokines have
20 been evoked by it, is there mitochondrial
21 involvement, is there apoptosis -- and it's much
22 more complicated than we thought.

1 This shows Ray Chung's (phonetic) study
2 of Fas ligand and HGF in patient with a variety of
3 etiologies. The APAP and the idiosyncratic DILI
4 cases typically have -- as well as Wilson's --
5 typically have the highest levels of cytokines.

6 Another issue that has been brought up
7 earlier is renal failure. These are the results
8 of looking at acute kidney injury in ALF in the
9 various etiologies and, again, there isn't time to
10 go into detail, but 34 percent of the APAP cases
11 had renal replacement therapy, meaning some form
12 of hemodialysis.

13 The bottom line for spontaneous survival
14 was, if you needed renal replacement dialysis, it
15 didn't always correlate with the severity of your
16 liver injury. It wasn't a bigger dose or a bigger
17 liver hit; it was sometimes totally out of sync.
18 The liver would be better, but the kidney would be
19 continuing to fail. But this group that required
20 RRT had worse spontaneous survival than the group
21 that did not require RRT, as you might expect.

22 And, again, coma grade and etiology were

1 the two factors that fell out as being independent
2 risk factors.

3 So, in summary, we feel that APAP
4 hepatotoxicity is still a very important problem
5 that dwarfs idiosyncratic drug reactions. The
6 narcotic compounds are involved in at least 40
7 percent. It comprises an additional 18 percent of
8 what are considered clinically to be
9 indeterminate. There's psych and drug abuse
10 issues in both the unintentional and the
11 intentional groups, of course. Multiple products
12 in at least 20 percent. Renal injury is common.
13 And there probably are other roles for concomitant
14 meds.

15 If the incidence is declining, it's only
16 modestly. This is still the largest cause of
17 death from ALF in the U.S.

18 What we're trying to do in the ALFSG is
19 to continue the registry. Obviously we'll put
20 some of the data I showed you into Larson II. We
21 now, following the lead of Keith Hawton, who I
22 think you will hear from tomorrow, have developed

1 a detailed questionnaire to ask the patients,
2 after they've awakened from their coma, to find
3 out exactly what they were taking and what they
4 thought. And although we've only done it on 20 so
5 far, I don't think we've found a single
6 unintentional case who thought that acetaminophen
7 had any indication of toxicity about it.

8 We're also trying to alert clinicians
9 that that hyper-acute picture of the ALT of 5,000
10 ought to importantly trigger considering NAC,
11 whether you have a clear-cut history, or even if
12 acetaminophen history is denied. But I think
13 Dr. James' assay, if it can get into the emergency
14 room at some future time, would be a great boon.
15 We're still looking at cytokines. And we're happy
16 to help and be included in the discussions today
17 and tomorrow, and in the future, in terms of
18 figuring out what to do with this complicated
19 product.

20 So thank you for your attention. I must
21 acknowledge all the sites in the ALFSG, as well as
22 all the people at NIDDK and UT Southwestern, and

1 our various grant support, and thank you for your
2 attention.

3 DR. NELSON: Thank you. Our next speaker
4 is Dr. Dan Budnitz from the Centers for Disease
5 Control and Prevention, to discuss
6 acetaminophen-related emergency department visits.

7 DR. BUDNITZ: Good afternoon. We just
8 heard a clinical perspective from Dr. Lee. Now
9 I'm going to start off giving a little bit of a
10 public health perspective by presenting some
11 findings on the national surveillance of
12 acetaminophen-related emergency department visits,
13 and then I'll end by presenting a little bit of
14 data on liver transplant listings related to
15 acetaminophen.

16 So as we know, the primary interest of
17 this committee is liver injury from
18 acetaminophen-containing products which may result
19 in deaths from hepatotoxicity, liver transplants,
20 hospitalizations, emergency department visits and
21 subacute effects. But as you know and we'll hear
22 more about, there are challenges in using national

1 public health surveillance data to identify
2 specifically liver failure from acetaminophen
3 products.

4 But we do have a bit more data -- a bit
5 more national data -- on acetaminophen overdoses
6 which I'll define, for this presentation, as
7 ingestion of more than the indicated amount, and
8 which we generally agree is the population that's
9 most at risk for liver injury.

10 However, as the committee knows, there
11 also can be adverse effects from acetaminophen
12 that are not necessarily dose-related, and there
13 also can be adverse effects from the products that
14 are mixed with acetaminophen in combination
15 products.

16 So I'm going to be addressing this kind
17 of middle level of the injury pyramid, these
18 emergency department visits, particularly ED
19 visits -- I'm going to start with adverse effects
20 of all types and then quickly focus in on
21 overdoses and then try to examine some risk
22 factors for these overdoses.

1 The data that I'll be using are from the
2 National Electronic Injury Surveillance System, or
3 NEISS, which is a national probability sample
4 consisting of 63 emergency departments across the
5 nation. And data from this system can be used to
6 calculate national estimates of total number of ED
7 visits. It's operated by the U.S. Consumer
8 Product Safety Commission, and has several
9 components, including one called the Collaborative
10 Adverse Drug Event Surveillance Project, which is
11 done in coordination with CDC and FDA, and then a
12 special self-inflicted harm study that was begun
13 recently in collaboration with the injury center
14 at CDC.

15 Now, in NEISS, data is collected in the
16 following way. A patient visits an emergency
17 department where they are treated, and the visit
18 is documented on the clinical chart. in the next
19 couple of days, a coder, employed by NEISS, will
20 review the charts and identify cases and abstract
21 data. The data are transferred to the Consumer
22 Product Safety Commission, or CPSC, and data are

1 validated by CDC.

2 Now, some key points is that these data
3 are based on the physician diagnosis in the
4 clinical ED chart. It's what we call active
5 reporting, meaning the clinician does not do
6 anything, other than care for the patient and
7 document as normal. And it's a surveillance
8 system. It does ongoing data collection.

9 Now, the case definition I'll use for
10 what I present is an emergency department visit in
11 which the treatment physician attributed to an
12 acetaminophen-containing product. These involve
13 what people have been calling unintentional
14 injuries, or adverse events, and these
15 specifically exclude recreational use or drug
16 abuse.

17 There also is the component of
18 intentional self-injury, or suicide or self-harm
19 attempts.

20 And we use very strict inclusion criteria
21 for our base estimates for the
22 acetaminophen-containing product. The

1 acetaminophen-containing product had to be
2 specifically identified as such.

3 So here are annual estimates of
4 acetaminophen-related emergency department visits
5 by cause. So this is from 2006 and 2007, but the
6 estimates are annualized.

7 We estimate at least 54,000 emergency
8 department visits due to self-harm attempts
9 involving acetaminophen products, about 18,000 ED
10 visits for side effects, about 14,000 ED visits
11 from allergic reactions, about 10,000 ED visits
12 for unsupervised child ingestions and about 13,000
13 ED visits for other unintentional overdoses. Now,
14 remember, somewhere in this mix are ED visits that
15 will result in liver injury. And now we'll focus
16 on the overdoses, which are most likely to cause
17 these.

18 So here we see the self-harm visits, the
19 child ingestions, and the other unintentional
20 overdoses, and some characteristics of each.
21 You'll see the national estimates I mentioned and
22 the number of cases that they're based on. We'll

1 see that this is a relatively young population, a
2 median age of 29 among the self-harm cases, and a
3 median age of 32 among the other intentional [sic]
4 overdoses.

5 It's a predominantly female population
6 for self-harm and other unintentional overdoses,
7 and we see a hospitalization rate of about 45
8 percent among the self-harm cases. These do not
9 include additional, 29 percent, that were admitted
10 for psychiatric evaluation.

11 We see relatively fewer number of
12 children where a proportion of children were
13 hospitalized, 9 percent, and 27 percent of folks
14 with other unintentional overdoses were
15 hospitalized.

16 In over half of cases of self-harm cases,
17 other non-acetaminophen-containing products were
18 involved, but these products were rarely involved
19 in child ingestions and involved in a quarter of
20 other unintentional overdoses.

21 And, finally, two or more different
22 acetaminophen products were involved in 6 percent

1 of cases of self-harm, 7 percent of child
2 ingestions and 10 percent of other unintentional
3 overdoses.

4 This is a figure that demonstrates a
5 little bit more detail about the number of ED
6 visits by age. You can see on the horizontal axis
7 we have the age ranges; on the vertical axis we
8 have, again, the annual estimated number of ED
9 visits in thousands. The pink is unsupervised
10 ingestions in children, largely younger child.
11 And then we see, in gray, the self-harm attempts,
12 and in the dark purple, the other unintentional
13 overdoses.

14 Now we can look at the ingredients
15 involved in emergency department for overdoses.
16 On the top line you see products that just involve
17 a single-ingredient acetaminophen product. We see
18 that makes up two-thirds of the child ingestions
19 and a little bit more than one-third of the
20 self-harm attempts and 27 percent of the other
21 unintentional overdoses. Opioid analgesic
22 combinations are involved in 45 percent of

1 self-harm cases and 55 percent of other
2 unintentional overdoses.

3 Other combination -- over-the-counter
4 combination products are used -- are involved a
5 little bit less frequently. And two or more
6 different types of acetaminophen products are
7 involved in 4 percent of self-harm cases and 4
8 percent of other unintentional overdoses.

9 Now I'll provide a few other details
10 about the particular causes of acetaminophen
11 overdoses.

12 We are able to look at the number of
13 pills that were involved -- or ingested in
14 emergency department visits for self-harm cases.
15 This is based on 1,280 of 1,857 cases -- or 69
16 percent -- where we had information about a pill
17 or bottle count.

18 You can see that most self-harm attempts
19 involved less than ten -- less than or equal to
20 ten pills, but then you can see the remainder of
21 the distribution. And this information might be
22 more useful after you hear additional information

1 from the UK.

2 Here's just quick example cases, because
3 you haven't heard too many cases yet today. This
4 is one of our cases of a 29-year-old female who
5 took a handful of Tylenol after drinking alcohol
6 in a suicide attempt. She was admitted -- a
7 psychiatric admission. And the case of a
8 42-year-old male who took an intentional drug
9 overdose of 80 Vicodin and 60 Fioricet in a
10 suicide attempt who was admitted to the intensive
11 care unit.

12 Some additional information on
13 unsupervised child ingestions. Even though only 9
14 percent of these children were admitted, 28
15 percent had significant treatment in the emergency
16 department, either decontamination, largely with
17 activated charcoal, or N-acetylcysteine in the
18 emergency department. 57 percent ingested a pill
19 or solid dose form, and 36 percent ingested
20 liquid; in 7 percent the dose form was unknown.

21 Here's an example case of a 22-month-old
22 male who ingested 10 to 12 caplets containing 500

1 milligrams of acetaminophen and 25 milligrams of
2 Benadryl. Some were chewed up and some were
3 dissolved. The childproof cap was not properly
4 latched. This patient was treated and released.

5 But there was another 20-month-old female
6 who drank a previously unopened bottle of Tylenol
7 medicine, and I guess she was taught to share, and
8 she shared it with her four-year-old sister. She
9 was treated with charcoal and then released.

10 Now let me move on to other unintentional
11 overdoses. Here we see the annual estimates of
12 emergency department visits for other
13 unintentional overdoses of acetaminophen products
14 by non-opioid-containing acetaminophen products in
15 the light purple and opioid-containing
16 acetaminophen products in the darker purple. I
17 think one important finding is that it's a
18 relatively similar number of ED visits,
19 approximately a thousand a year, for each adult
20 age group there, roughly each decile.

21 On the other hand, there's a question
22 from the committee about adolescents and young

1 adults. We find, when we look at the non-opioid
2 acetaminophen products, 60 percent of these visits
3 involved patients aged 12 to 29 years old.

4 When we look a little bit more about the
5 underlying causes of these emergency visits for
6 unintentional overdoses, we find that 39 percent
7 reported on the ED clinical chart taking
8 additional doses for additional symptom relief.
9 That's about 5,000 estimated ED visits annually
10 attributed to this activity by patients. And 57
11 percent of these folks were 12 to 29-year-olds.

12 Another 6 percent of other unintentional
13 overdoses involved confusing bottles by the
14 patient, taking acetaminophen products by mistake.

15 And then we looked for other underlying
16 causes -- and these were less common. 15 cases --
17 too few to make a national estimate -- of taking
18 medication prescribed for another person, two
19 cases of pharmacy dispensing errors, and one
20 documented case of a caregiver confusing infant
21 and child formulations.

22 Here are a few example cases. A

1 15-year-old female who took 12 to 16 Tylenol
2 Cold/Sinus for a headache. She states she didn't
3 want to hurt herself, but didn't know that that
4 much could hurt her. She was given charcoal,
5 observed and then released.

6 And another case was an 18-year-old male
7 who had back pain and wanted to play soccer this
8 afternoon, so he took more Tylenol. Now with
9 epigastric pain and hyperventilation. Had an
10 acetaminophen level of 132. Was treated with
11 activated charcoal, Mucomyst and admitted.

12 And finally a case of an 82-year-old
13 female who was confused and took nine Vicodin
14 instead of one Vicodin and eight of her other
15 medicines and was unable to be aroused. Treated
16 with Narcan and admitted.

17 So a couple of limitations I want to
18 highlight is that these, again, are ED visits for
19 overdoses, not necessarily all of them for
20 hepatotoxicity. Also, as you saw in the last
21 case, for combination products, the primary
22 manifestation for overdose may not be

acetaminophen toxicity per se.

We get our data from abstraction of the ED clinical record, so it's limited just to what might be documented in the emergency department.

But we did -- and we also narrowly defined acetaminophen product exposure to just -- whenever a product was specifically noted to be an acetaminophen-containing product. We also do not have data on the subsequent hospitalizations or long-term follow-up.

But my hope is that the committee can use some of these data as they recommend national intervention strategies.

So I'm just going to highlight a few of these points that might be useful for the committee, and that is among the ED visits for intentional self-harm, suicide attempts, 72 percent of folks ingested less than 25 pills, 53 percent ingested less than 16 pills. Again, data that might be useful in the context of what we hear more about tomorrow.

Among emergency department visits for

1 child ingestions, 57 percent ingested pills or
2 solid dose forms. And among ED visits for other
3 unintentional overdoses, 39 percent of patients
4 knowingly took extra amounts above the recommended
5 dose.

6 To get some perspective on burden,
7 unsupervised child ingestions are nearly as common
8 as all other unintentional overdoses, but these
9 children are less likely to be hospitalized.

10 Among the ED visits for other
11 unintentional overdoses, of the 39 percent that
12 knowingly took extra amounts, most of these
13 patients were teenagers or young adults. And ED
14 visits for dosing confusion were less commonly
15 reported, about 40 [sic] percent attributed to the
16 use of two acetaminophen products from two
17 different classes, but I should note about 10
18 percent were use of two different acetaminophen
19 products which may have been from the same class
20 or not.

21 Among ED visits for intentional self-harm
22 and other overdoses, 50 percent involved

1 combination products, but again, much fewer
2 involved two or more acetaminophen products.

3 Among ED visits for unsupervised child
4 ingestions, most involved single-ingredient
5 acetaminophen products. And documented cases of
6 overdoses for mis-dosing of infant formulations
7 were rare, but did indeed occur.

8 I'd also like to encourage the committee,
9 as you deliberate on interventions, to think about
10 how whatever intervention that might be
11 recommended would be evaluated for its impact in
12 effectiveness.

13 And now, finally, I'll present briefly
14 some data on acetaminophen-related liver
15 transplant listings. My colleague, Dr. Priti
16 Patel, compiled most of these data.

17 And this is to identify that -- a little
18 trapezoid in our injury pyramid of acetaminophen
19 and liver transplants.

20 We collected data from the Organ
21 Procurement and Transplant Network, or OPTN, which
22 is operated by the United Network for Organ

1 Sharing. And this really isn't designed to be a
2 surveillance system; it's designed as a system to
3 register patients and match organs. So there is
4 no specifically diagnosis code for
5 acetaminophen-induced liver failure, and no
6 specific element for medication name.

7 So what we did was we did a manual search
8 of acetaminophen products listed in the other
9 diagnosis text field, and identified 555
10 acetaminophen-related transplant listings between
11 2004 and 2008. This was just 1 percent of
12 listings for all liver transplants for this time
13 period.

14 We see a similar young age, median age of
15 29, and 17 cases, or 3 percent, were among
16 children less than or equal to five years old.
17 They're predominantly female, and these patients
18 were quite sick. 60 percent were on life support
19 at the time of listing.

20 Of these patients, 25 patients died
21 awaiting transplant or their condition
22 deteriorated, 37 percent were transplanted, and

1 for 36 percent their condition improved, while a
2 few remain on the list and 2 percent refused
3 transplant for other reasons.

4 These are the liver transplant listings
5 related to acetaminophen by year for 2004 to 2008.
6 In purple you see the total number, and in the
7 blue line you see a percentage of the total number
8 of liver transplant listings that year. These
9 data showed no significant trend over time by
10 weighted linear regression or logistic regression.

11 So, in summary, approximately 1 percent
12 of liver transplant listings for
13 acetaminophen-related -- are for
14 acetaminophen-related liver failure. That's about
15 111 patients listed annually for the past five
16 years. But we have to remember that the OPTN
17 database was not designed for surveillance. It
18 has important limitations in identifying cases of
19 the specific drugs involved, and no information,
20 really, on risk factors or underlying causes.

21 I'd like to thank my colleagues at the
22 CDC and our other federal agencies, and also the

1 United Network for Organ Sharing. Thank you.

2 DR. NELSON: Thank you. Our next speaker
3 is Dr. William Bower, from the Centers for Disease
4 Control and Prevention, to provide us with some
5 CDC data on acute liver failure from
6 acetaminophen.

7 DR. BOWER: Good afternoon, everyone.
8 So, again, I'm Commander William Bower, and I
9 currently work in the Office of Blood, Organ and
10 Tissue Safety; however, the FDA wanted me to
11 present some work that I did when I worked in the
12 Division of Viral Hepatitis, so that's what I'm
13 going to present.

14 First, the disclaimer that the CDC asked
15 us to show, which is that the findings and
16 conclusions in this presentation are mine and do
17 not necessarily represent the official position of
18 the Centers for Disease Control.

19 So the study that we designed back in
20 2000 and conducted from 2000 to 2004 was a
21 surveillance system that could be used to better
22 characterize the epidemiology of acute liver

1 failure in the United States. It was to identify
2 all cases of acute liver failure in a defined
3 geographic region, collect clinical and
4 epidemiological information, obtain specimens for
5 diagnostic and research studies. Another
6 objective was to identify etiologies of acute
7 liver failure and, of these etiologies, to
8 characterize cases of known and unknown etiologies
9 and provide demographic and clinical features and
10 exposure and potential risk factors.

11 So the methods for this study were that
12 we conducted population-based surveillance for
13 acute liver failure within the eight counties that
14 comprise the metropolitan Atlanta area between
15 November 2000 and October 2004. And there are 26
16 acute care hospitals in the eight-county metro
17 Atlanta area, and we were able to get 24 to
18 participate, which accounted for 95 percent of the
19 ICU beds in the metro Atlanta area. So our
20 definition for acute liver failure was defined as
21 the presence of coagulopathy, or an INR of greater
22 than 1.5, any grade of hepatic encephalopathy

1 within 26 weeks of the onset of the illness, and
2 no history of underlying liver disease, which --
3 this case definition is very similar to the one
4 that Dr. Lee's group used -- or exactly the same.

5 A questionnaire was administered, and
6 medical records were reviewed to determine
7 clinical features, etiologies and outcomes. And
8 for the purpose of this committee meeting, I
9 wanted to highlight this, that the diagnosis of
10 acetaminophen toxicity required a toxic serum
11 acetaminophen level based on a toxicity nomogram
12 or a history of ingestion in excess of therapeutic
13 dose. And then when we talk about intentional
14 versus accidental use, the intentional
15 acetaminophen overdose was based on stated intent
16 by the patient or by an inpatient psychiatric
17 evaluation.

18 So now the results of the study. You can
19 see that we enrolled 65 patients, 59 adults, 16
20 children. The ages of the adults were from 18 to
21 77 years, and -- with an average of 38. And the
22 children's average age was 3.5, ranging from 3

1 days to 14 years. You can see the percentage male
2 there. And I need to point out for the committee
3 members that the handouts -- I changed these.
4 There was a typographical error in this, so these
5 numbers that represent the percentage of the race
6 for adults are different in your handouts. But
7 you can see the demographics here.

8 And the death for adults, 23 of the adult
9 patients died, or 47 percent, where only three, or
10 19 percent, of the children -- and for the
11 purposes of the committee here, I teased out the
12 acetaminophen-related deaths, which were 7 of the
13 23, or 30 percent. And it was two for the
14 children -- two of the three deaths in children
15 were acetaminophen-related, or 66 percent. But
16 then, again, this is very small numbers.

17 So here are the findings on -- of the
18 distribution of etiology in adults, that 46
19 percent were acetaminophen-related, followed by 16
20 percent with drug-induced. Then you can see the
21 other -- viral hepatitis, autoimmune and unknown
22 etiology -- were all equal at 10 percent.

1 Ischemic was 6 percent, and then other were 2
2 percent.

3 And then if you take this slice of the
4 pie and break it down, you get that there were --
5 45 percent were intentional overdoses, and then
6 the other 55 percent that were considered
7 accidental were distributed evenly between ones
8 where alcohol was considered to potentially play a
9 role -- and then the other portion there where
10 alcohol was not felt to be a contributing factor.

11 So now, in the children -- again, there
12 were 16 children enrolled, and the largest
13 etiology in the pediatric group was unknown, at 38
14 percent, followed by acetaminophen-related at 25
15 percent. And all of these 25 percent were
16 unintentional.

17 So now, because this was a
18 population-based study in a defined geographic
19 area, we're able to give some estimates, so the
20 study population base was 3.3 million in the
21 eight-county area that comprises metro Atlanta.
22 And of the 65 total cases over the period of time,

1 gave an annualized acute liver rate of 5.5 per
2 million.

3 And then if you apply this to the entire
4 U.S. population, which was about 290 million at
5 the time that this study was done, that gives
6 approximately 1600 acute liver failure cases per
7 year. And then if you extrapolate that to about
8 40 to 45 percent of these cases -- of the total
9 acute liver failure cases are related to
10 acetaminophen, that gives you about 640
11 acetaminophen-related acute liver failure cases
12 each year. And compare this to the other drugs
13 would -- or the non-acetaminophen-related drugs of
14 123 cases per year.

15 So now this study did have some
16 limitations. It was conducted only in one
17 geographic area, and the metro Atlanta area does
18 have some demographic differences than the rest of
19 the United States. The population in the metro
20 Atlanta area is younger, and there are more blacks
21 in the metro Atlanta area, so the generalizability
22 of these findings to the rest of the United States

1 is not known; however, it did compare quite well
2 to Dr. Lee's numbers.

3 The -- there was probably underreporting
4 in our study because we were confident that each
5 case we enrolled was a true case of acute liver
6 failure, but we probably did not capture all of
7 the cases that came into the ICUs, even though we
8 did have dedicated staff in the intensive care
9 units, and we did contact them one to two times a
10 week, and we did do review of ICU logs -- we
11 probably did miss some cases.

12 And then if a case did reside in the
13 metro Atlanta area, but went to a hospital outside
14 the metro Atlanta area, we wouldn't have captured
15 them. So I would say that our calculated incident
16 would have to be considered a low estimate.

17 And then, as someone from the
18 pharmaceutical company stated before, these
19 patients with acute liver failure by definition
20 all have some degree of altered mental status, so
21 the exposure history sometimes had to be obtained
22 from the family, and that also limited our ability

1 to collect accurate data on medication intake
2 prior to onset of illness.

3 So, in summary, this was -- to our
4 knowledge at the time, this was the first
5 population-based study of acute liver failure
6 conducted in the United States. It provides
7 information on how generalizable results from
8 tertiary care centers, such as the ones that
9 Dr. Lee's study spoke to, are -- how these are
10 generalizable to the general population.

11 The distribution of etiologies and
12 spontaneous survival rates in our study were
13 similar to those found in the larger tertiary care
14 base studies; however, we did find that
15 acetaminophen-related acute liver failure was more
16 common among those that were transferred to liver
17 transplant centers, so the percentage of acute
18 liver failure at the tertiary care studies [sic]
19 possibly may be shifted a little bit more towards
20 the acetaminophen cases.

21 Acetaminophen-related acute liver failure
22 is the most common etiology of acute liver failure

1 in the United States in our study as well as
2 what's reported to liver transplant centers,
3 approximately 40 to 45 percent being acute liver
4 failure, and about half of those are unintentional
5 overdoses.

6 Unintentional acetaminophen was also --
7 overdose was also the second most common in --
8 acute liver failure in children, accounting for
9 about 25 percent. And then, if you extrapolate
10 the numbers from this study to the U.S.
11 population, acetaminophen accounts for
12 approximately 640 cases of acute liver failure
13 each year.

14 Thank you.

15 DR. NELSON: Thank you.

16 Our next speaker is Angelika
17 Manthripragada, an epidemiologist from the Office
18 of Surveillance and Epidemiology at FDA, to
19 discuss the characteristics of acetaminophen
20 overdose and related hepatotoxic events.

21 DR. MANTHRIPRAGADA: Good afternoon. My
22 name is Angelika Manthripragada. I'm from the

1 Office of Surveillance and Epidemiology. Today I
2 will be presenting results of analyses
3 characterizing acetaminophen overdose and related
4 hepatotoxic events.

5 The objectives of our research were
6 three-fold. First, to characteristics the
7 intentionality of acetaminophen overdoses and to
8 provide national estimates of emergency department
9 visits and hospitalizations that result.

10 Second, we also aimed to describe the
11 burden of acetaminophen-associated calls to the
12 National Poison Data System.

13 And our third objective was to provide a
14 perspective on the magnitude of liver toxicity
15 associated with acetaminophen in the United States
16 and to characterize unintentional overdoses.

17 To achieve the first objective, we
18 utilized two publicly available data sources,
19 first the National Hospital Ambulatory Care
20 Survey, which concerns ED visits. For these
21 analyses, we calculated weighted frequencies of
22 visits.

1 Second, we also used the National
2 Hospital Discharge Survey, which captures
3 inpatient hospital discharges. We calculated
4 age-adjusted hospitalization rates and also crude
5 hospitalization rates by intentionality, using the
6 U.S. population as a denominator.

7 Both data sources are probability survey
8 samplings of visits made to non-federal general
9 short-stay hospitals in the United States.

10 The slide presents the definitions we
11 used in our analyses. For both HAMCS and NHDS, we
12 used ICD-9 codes to define visits related to
13 acetaminophen poisoning. This includes all
14 overdose visits coding as acetaminophen poisoning
15 regardless of the outcome of the visits.

16 For HAMCS, intentionality was defined
17 using ICD-9 -- using a survey question, whereas,
18 for NHDS, we had to rely on ICD-9 codes.

19 For NHDS, intentional overdoses were all
20 hospitalizations coded for acetaminophen poisoning
21 and also for suicide or overdose due to other
22 substances. Unintentional overdoses were all

1 hospitalizations coded for acetaminophen poisoning
2 and accidental overdose, with no indication of
3 suicide, overdose due to other substances, or
4 depressive disorder. All other acetaminophen
5 visits were defined as undetermined.

6 This slide concerns emergency department
7 visits relating to acetaminophen overdose. The
8 average number of visits per year for the period
9 of 2000 to 2006 was 42,329. Of this, nearly 52
10 percent were unintentional, and close to 46
11 percent were intentional, with the remaining being
12 classified as undetermined. Please note that
13 these visits include all acetaminophen
14 overdose-related visits, not just those resulting
15 in acute liver toxicity.

16 This slide concerns hospitalizations
17 related to acetaminophen overdose. We calculated
18 the rate of acetaminophen overdose-related
19 hospitalizations by age and sex in the United
20 States for the period of 1991 to 2006. Females
21 under 30 years of age had the greatest rate of
22 acetaminophen overdose-related hospitalizations

1 compared to other age/sex groups throughout the
2 years. Overall, men have a lower rate of
3 acetaminophen overdose-related hospitalizations
4 than women.

5 The rate of acetaminophen
6 overdose-related hospitalization does not appear
7 to be decreasing in any age/sex group.

8 In this slide we present the frequency of
9 hospitalizations by year. In 2005 and 2006, there
10 were an average of 37,345 hospitalizations with a
11 lower bound of the 95 percent confidence interval
12 being 32,164, and the upper bound 42,527.

13 We calculated the age-adjusted rate of
14 acetaminophen overdose-related hospitalizations
15 standardized to the 2000 U.S. population among
16 those aged ten and older for the period of 1991 to
17 2006. The point estimate for the rate of
18 acetaminophen poisonings in 2005 to '6 was 15.68
19 per 100,000 U.S. population. This is the highest
20 for the entire period between 1991 to 2006.

21 These analyses suggest that there is no
22 decrease in acetaminophen overdose despite the

1 launch of the educational campaign in 2004.

2 We calculated the crude rate of
3 acetaminophen overdose-related hospitalizations in
4 the United States by intentionality for the period
5 of 1991 to 2006. Over this period, neither the
6 rate of intentional nor unintentional
7 hospitalizations decreased.

8 Our analyses of emergency department and
9 hospital data were limited by a number of factors.
10 First, we could not report or project data with
11 crude counts less than 30, since these estimates
12 are considered unreliable regardless of the
13 magnitude of the standard error.

14 Related to this is the limited liver
15 toxicity data. The crude counts for liver
16 toxicity were under 30 for almost every year
17 between 1991 to 2006, and so could not be reported
18 or projected. Thus, our estimates represent all
19 overdoses and not necessarily those resulting in
20 liver toxicity.

21 Additionally, we had no information on
22 the type of product.

1 Lastly, intentionality was difficult to
2 ascertain for both emergency department and
3 hospital data. The social stigma associated with
4 suicide may result in misclassification of
5 intentional cases as unintentional.

6 On the other hand, accidental visits are
7 coded using E-codes, and these E-codes are
8 incompletely reported in NHDS due to differential
9 reporting requirements by state.

10 The next section of this presentation
11 pertains to our second objective, which is to
12 describe the burden of acetaminophen-associated
13 calls to the National Poison Data System, or NPDS.
14 NPDS is a poisoning surveillance database
15 maintained by the American Association of Poison
16 Control Centers in cooperation with 61 poison
17 control centers in the United States.

18 This database has a repository of over 45
19 million human poison exposures, and the
20 participating centers served approximately 305
21 million of the U.S. population in 2007.

22 We reviewed the center's annual reports

1 from 2003 to 2007 and determined the number of
2 acetaminophen-related calls, and also the number
3 of calls resulting in fatality. For fatality, we
4 included only cases listing acetaminophen as the
5 primary agent.

6 This slide summarizes the definitions
7 used to define acetaminophen-related fatalities
8 and intentionality. In overdoses included the
9 category suspected suicide, intentional abuse and
10 intentional unknown. Unintentional overdoses
11 included unintentional general, intentional
12 misuse, unintentional misuse, therapeutic error
13 and adverse drug reaction.

14 In 2005, acetaminophen
15 poisoning-associated calls represented 5 percent
16 of all calls to poison control centers. There was
17 a slight increase in acetaminophen
18 poisoning-related calls from 2003 to 2005. In
19 2005, approximately 61,000 calls required
20 treatment in healthcare facilities, which include
21 acute care hospitals, physician offices or clinics
22 and free-standing emergency centers.

1 Approximately 2,700 calls were related to
2 signs and symptoms that were life-threatening or
3 resulted in significant disability.

4 Approximately 43,000 involved children
5 under six years of age, and approximately 70,000
6 calls involved unintentional exposures.

7 In 2005, 214 acetaminophen-associated
8 fatalities were reported to the NPDS, and this
9 increased to 224 by 2007. In fact, the total
10 number of fatalities in association with
11 acetaminophen has been around 200 in the last five
12 years, with a slight dip in 2005 when the total
13 number was 188.

14 In 2007, acetaminophen represented 18
15 percent of the total fatalities reported to NPDS.
16 Of the 224 fatalities in 2007, acetaminophen was
17 undoubtedly responsible in 55 percent of cases,
18 probably responsible in 37 percent of cases, and
19 contributing in 8 percent of cases.

20 This chart gives a breakdown of
21 intentionality among the 224
22 acetaminophen-associated fatalities reported in

1 2007. 69 percent of the cases were intentional,
2 19 percent were unintentional. In 12 percent of
3 cases, the cause was unknown or was not reported.

4 This chart describes the number and types
5 of acetaminophen products that were associated
6 with unintentional fatalities. 46 percent of
7 deaths occurred in individuals who took a single
8 over-the-counter acetaminophen product. 42
9 percent of fatalities occurred in individuals who
10 took one prescription acetaminophen product. And
11 in 12 percent of cases, two acetaminophen products
12 were taken concomitantly.

13 A limitation of this analysis is that
14 serious poisoning cases may go directly to
15 emergency departments and are, therefore, not
16 captured by poison control centers, resulting in
17 extensive underreporting. Furthermore, chronic
18 users may be less likely to call the poison
19 control center and, thus, not be captured.

20 The final section of this presentation
21 pertains to objective 3, which is to provide a
22 perspective on the magnitude of liver toxicity

1 associated with acetaminophen in the United States
2 and to characterize unintentional overdoses using
3 examples of cases. To do this, we used the
4 Adverse Event Reporting System, or AERS. We
5 determined the most common drugs associated with
6 liver failure from 2004 through 2008. We also
7 present key findings from a review of
8 acetaminophen and hepatotoxicity completed in
9 2002. Lastly, we characterize unintentional
10 overdoses using representative cases.

11 We evaluated which drugs in the AERS
12 database had the highest number of reports of
13 liver failure between 2004 and 2008.
14 Acetaminophen continues to be the number one drug
15 associated with liver failure for every year from
16 2004 to 2008. Additionally, AERS continues to
17 receive reports of liver toxicity and death
18 associated with acetaminophen.

19 A detailed AERS review of hepatotoxicity
20 was conducted in 2002 for the previous advisory
21 committee meeting. The key findings from that
22 review are as follows.

1 There were 307 cases of liver injury
2 reported in the U.S. between 1998 to 2001,
3 excluding suicides. 60 percent of these had
4 severe life-threatening liver injury and liver
5 failure, with 40 percent resulting in death.

6 Higher than recommended doses were
7 reported more frequently than recommended or lower
8 than recommended doses among the 134 cases which
9 reported a dose.

10 Among adults who reported daily doses,
11 the mean daily dose was 6.5 grams, with the median
12 daily dose increasing with the severity of hepatic
13 injury. 41 percent reported taking more than 4
14 grams per day.

15 Acetaminophen-narcotic combinations were
16 the most commonly implicated product, and 25
17 percent reported the use of more than one
18 acetaminophen product.

19 There were 25 pediatric cases. 84
20 percent of these involved medication errors. Most
21 reported the use of only acetaminophen product
22 with over-the-counter single-ingredient

1 acetaminophen being the most commonly implicated
2 product.

3 Here is a represented AERS case of an
4 unintentional overdose for the use of more than
5 one acetaminophen-containing product that resulted
6 in death. A 13-year-old girl was reportedly
7 taking two acetaminophen-containing products for
8 five days to treat the symptoms of an upper
9 respiratory infection and minor pain. The
10 acetaminophen dose was estimated to be
11 approximately 6 to 7 grams per day. The patient
12 was found to have elevated transaminases and
13 bilirubin, prolonged INR and an acetaminophen
14 level of 74.6 micrograms per milliliter. She
15 progressed on to encephalopathy and had declining
16 renal function.

17 She denied any intentionality of
18 self-harm, and there was no history reporting
19 self-harm. She denied exposure to potentially
20 hepatotoxic substances. Her past medical history
21 was significant for a kidney transplant, and her
22 concomitant medications included immunosuppressive

1 therapy.

2 Upon presentation, she was treated with
3 N-acetylcysteine and placed on a transplant list,
4 but died prior to receiving one.

5 I will describe another representative
6 AERS case of an unintentional overdose from
7 multiple products containing acetaminophen that
8 occurred in an institutional setting. A
9 33-year-old hospitalized female was being treated
10 for community-acquired pneumonia when she
11 developed elevated transaminases, LDH and Alkaline
12 phosphase.

13 Tests for other etiologies of liver
14 disease were negative.

15 A review of her medication profile
16 revealed that there were several
17 acetaminophen-containing medications that were
18 active, and she unintentionally received up to 6.2
19 grams per day for an unspecified number of days.

20 All acetaminophen products were
21 discontinued, and her transaminases returned to
22 normal.

1 This last representative AERS case is of
2 an unintentional overdose that occurred from the
3 lack of pain relief. A 33-year-old male with an
4 impacted wisdom tooth was taking over-the-counter
5 analgesics for pain relief. He first tried
6 ibuprofen, without relief, and then switched to
7 acetaminophen. He started taking one to two
8 tablets of the 500-milligram extra-strength tablet
9 every one to two hours for two days, but without
10 relief.

11 He then increased the dose to two to four
12 tablets every one to two hours for one day. It
13 was estimated that the patient consumed over 12
14 grams per day.

15 He presented to the emergency department
16 with pain, nausea and malaise. His LFTs were
17 reportedly normal. He was treated with activated
18 charcoal and N-acetylcysteine and discharged after
19 three days.

20 Among the commonly recognized limitations
21 of AERS data are extensive underreporting of
22 cases, no appropriate denominator data and

1 variable quality of reports.

2 Also, the causality of the drug-event
3 association is often called into question, and
4 there is also an issue with reporting bias. For
5 example, how long a drug has been on the market,
6 the notoriety of a drug, or the media attention a
7 drug is receiving can affect the rate of
8 reporting.

9 In conclusion, the results of our
10 analyses can be summarized as follows.

11 Regarding objective 1, 52 percent of
12 emergency department visits were classified as
13 unintentional, 42 percent intentional, with the
14 remaining being classified as undetermined. We
15 noted no decrease in the rate of hospitalization
16 due to intentional or unintentional overdose,
17 despite the launch of the 2004 educational
18 campaign.

19 Regarding objective 2,
20 acetaminophen-associated fatalities represented
21 nearly 20 percent of all fatalities reported to
22 NPDS, with approximately 20 percent of these

1 fatalities being a result of unintentional
2 overdose.

3 In approximately 5 percent of
4 unintentional fatalities, two acetaminophen
5 products were taken concomitantly.

6 Regarding objective 3, according to crude
7 AERS data, acetaminophen continues to be the
8 number one drug associated with reports of liver
9 failure in the United States, with AERS continuing
10 to receive reports of liver toxicity and death
11 associated with acetaminophen.

12 This concludes my presentation. Thank
13 you.

14 DR. NELSON: Thank you.

15 Okay. So we're now up to a point at
16 which we have some time to ask speakers some
17 questions from the committee. Now, we have a list
18 of about six or eight people from before who had
19 questions, but I actually was hoping what we could
20 do would be to focus on the past several speakers
21 and see if there are any questions directed at
22 them, because that information is fresh in our

1 mind. Presumably, there will be questions. And
2 if we get through those quickly, we'll go back to
3 the others. Otherwise, all those people who are
4 on the list will clearly be able to ask questions.
5 And hopefully we'll get through those even by the
6 end of the day, in the last committee question
7 session.

8 Okay.

9 DR. FARBER: Neil Farber from UC San
10 Diego. For Dr. Manthripragada, you mentioned on
11 slide 21 that there were -- 41 percent of patients
12 reported more than 4 grams per day of
13 acetaminophen. Does that mean that there were 60
14 percent who reported less than 4 grams per day?
15 Or does that mean that you just don't have data on
16 the other 60 percent?

17 DR. CAO: Hi. Kelly Cao from Office of
18 Surveillance and Epidemiology. That data was
19 based on an AERS review that we had done for a
20 prior AC back in 2002, and the percentage comes
21 from the number of cases that reported a dose, and
22 I believe on the slide the N was provided. So

1 there were many cases that didn't provide a dose.

2 DR. FARBER: The question I had was, were
3 there cases who reported less than 4 grams per
4 day?

5 DR. CAO: I believe there were, although
6 I'd have to go back to the data to be certain of
7 it.

8 DR. NELSON: Dr. Kramer?

9 DR. KRAMER: Judith Kramer. I have a
10 question for Dr. Lee. In the profile of the whole
11 cohort, you described a pattern where the
12 bilirubin was less elevated than with other
13 drug-induced liver injury. Am I correct about
14 that?

15 DR. LEE: That's correct.

16 DR. KRAMER: And I just wondered -- this
17 is not my area of expertise, but I'm wondering if
18 you could comment about whether that raises any
19 question about the reassurance we heard from
20 Dr. Dart with regard to the fact that the small
21 studies they did had not found, quote, Hy sign
22 with the elevated bilirubin along with the ALTs.

1 DR. LEE: Right. I think when you see
2 this very hyper-acute injury that's only -- when
3 we gather the initial data, the bilirubin will
4 only be -- median value of 4.5, something like
5 that. But the aminotransferases are very, very
6 high.

7 Now, over time, they will also either
8 resolve or die within about another three days, or
9 get transplanted. So there are only a very small
10 fraction, maybe 5 percent, that will linger on for
11 two weeks, let's say. Then, of course, their
12 bilirubins will go up.

13 So I would say -- well, 4.5 is enough to
14 be a Hy's law case technically, but you're right,
15 it's not long enough in duration to build up the
16 bilirubin which sort of accumulates over time if
17 you have a moderately severe injury.

18 DR. KRAMER: So were you reassured by
19 Dr. Dart's presentation? I mean, there seems to
20 be a conflict between what he presented to us and
21 what we heard from the acute liver failure
22 injury --

1 DR. LEE: Again, he's looking mostly at 4
2 grams or less. We don't think there are too
3 many -- we agree with them that there are very few
4 cases under 4 grams. Most times people are taking
5 at least 6 grams per day and, as I showed,
6 frequently much more than that. So it's more a
7 matter of what's the quantity that they're putting
8 in, rather than looking at the edges with three
9 grams a day, four grams a day. You may have
10 aminotransferases, but you're not going to have a
11 big hit, except rarely if someone is
12 idiosyncratically susceptible.

13 DR. KRAMER: Thank you.

14 DR. NELSON: Dr. Todd?

15 DR. TODD: This question is for Dr. Lee
16 as well. I had a question about some methodology
17 of the acute liver failure study group. In terms
18 of attribution to acetaminophen, what's the
19 methodology you use? What measures of
20 reliability, and how to you adjudicate
21 disagreements when those arise?

22 DR. LEE: Okay. So the site investigator

1 is the primary clinician, and he attributes the
2 case to acetaminophen. In the Larson paper, we
3 used three criteria. One was -- which I think we
4 showed. One was ALT greater than 1,000 with a
5 history of acetaminophen. One was any level of
6 acetaminophen plus the picture of acute liver
7 failure. And the third was if you had a
8 compelling history.

9 DR. TODD: And were attempts made to look
10 at inter-observer variability or reliability when
11 you did this? Or a single observer adjudicated
12 everything?

13 DR. LEE: No. So we queried the sites
14 from the central data coordinating center for lack
15 of specific values, like did they not have an
16 acetaminophen parent compound level and so forth.

17 I would say that the verification for it
18 is in the data that I showed in the adducts
19 study -- maybe it's going backwards, but in a way
20 it substantiates -- and, again, when we went back
21 and looked at either the indeterminates or the
22 ones who were adduct-negative but who had been

1 adjudicated by the site investigator and by
2 myself, let's say -- or Dr. Larson -- as being
3 bona fide cases, we only had 11 out of whatever it
4 was -- 199 -- that didn't make the cut in terms of
5 their adduct level, and as I said, most of them
6 were late presenters.

7 DR. TODD: Thanks.

8 DR. NELSON: Dr. Wolfe?

9 DR. WOLFE: A question for Dr. Lee again.
10 Interesting presentation. I've admired your work
11 for a long time. This morning, towards the end of
12 the industry presentation, there seemed to be some
13 effort to downplay the significance of the adduct
14 findings. I think the remark was made more or
15 less than the presence of these adducts shouldn't
16 be viewed as liver damage but merely the presence
17 of the drug. I mean, certainly the specificity of
18 it looks like it is the presence of the drug.

19 Could you just comment on how you would
20 characterize the presence or meaning of the
21 adducts -- these studies that Dr. James and you
22 have done?

1 DR. LEE: Yeah. I may need to lean on
2 Dr. James for some of this, but I think what it --
3 the adduct really is NAPQI covalently bound to
4 cell proteins. Then she hydrolyzes off the cell
5 proteins. It's not a metabolic product. It's the
6 toxic unit --

7 DR. WOLFE: So you call it a toxic unit,
8 then?

9 DR. LEE: -- that's in the serum. Now,
10 you can say, oh, okay, so with a therapeutic dose,
11 you had .3 nanomoles. We're not looking at that
12 level. We're looking above. And I think you can
13 see -- and Dr. Dart's data showed that most of his
14 levels, when they looked at adducts in Dr. James'
15 assay, were at the .3 level. We didn't even begin
16 counting, based on her ROC curve, until it was
17 above 1.0.

18 DR. WOLFE: So you would agree, then,
19 that the adducts are some measure of liver
20 toxicity.

21 DR. LEE: Yes. Now, what we haven't done
22 is look in somebody, let's say, who had a Ketek

1 hepatotoxicity and a little bit of acetaminophen
2 as well, or viral hepatitis and a little
3 acetaminophen as well. We actually have looked a
4 little bit at the viral hepatitis, and it's kind
5 of confusing so far. I'm not sure we have a clear
6 message for that. We haven't looked at, let's
7 say, an idiosyncratic case that also got some
8 Tylenol. My guess is that it's a sheer quantity
9 effect and that you wouldn't see NAPQI bound to a
10 significant quantity if you, let's say, took 3
11 grams of acetaminophen but you were really in the
12 middle of a Ketek holocaust.

13 DR. WOLFE: Okay. I had other questions
14 for the FDA. In the data that you just presented,
15 some of which had been presented at the 2002
16 meeting, you found that -- something over half of
17 the patients in the AERS database had taken levels
18 of 4 grams or less -- and the median, I think, was
19 5 grams.

20 Do you have any further breakdown as to
21 what the range of doses or estimated doses were in
22 those people who were below the median, as in

1 below 5 grams?

2 DR. CAO: I have the range. The lower
3 range is 650 milligrams a day, but I don't have
4 the exact number of cases that reported taking a
5 dose less than 4 grams a day.

6 DR. WOLFE: Okay. Thank you.

7 DR. NELSON: Dr. Stergachis.

8 DR. STERGACHIS: This is for Dr. Budnitz.
9 The second largest category of emergency
10 department visits was for side effects, 17
11 percent. And it indicates here, under one of the
12 definitions, not excessive amounts. And I'm
13 curious to find out whether there were any liver
14 toxicities notes amongst that 17 percent that were
15 side effects to acetaminophen.

16 DR. BUDNITZ: I would have to look
17 specifically for that. I think that -- to look
18 for liver toxicity, we could do that. I don't
19 have that data before me.

20 DR. NELSON: Dr. Krenzelok.

21 DR. KRENZELOK: Thank you. Krenzelok.

22 Dr. Lee, a question for you. In your

1 presentation you suggested to us that
2 acetaminophen was not a safe drug. I think that's
3 kind of the way you characterized it. Dr. Kramer
4 asked you a question about toxic doses, and I
5 think you suggested that certainly most of your
6 cases were 6 grams or above and that you rarely,
7 if ever, saw them at less than 4 grams.

8 Is there a point where you would opine
9 that acetaminophen is a safe drug, or that you
10 think would be a reasonable safe dose for people
11 to take?

12 DR. LEE: I guess I'd rather not be
13 pinned down. That's a tough one. I think the
14 large bulk of the cases are cases where someone is
15 using it willfully, perhaps unintentionally, as
16 you saw in the specific cases near the end, not
17 aware of any harm with doses way above 4 grams.

18 I don't know that we're going to see
19 cases. We had, in the original ALF study group --
20 in the Larson paper, there are some cases that are
21 under 4 grams, but again, we've talked already
22 today about the history-taking is -- can be very

1 poor. And I would tell you, I think from some of
2 Dr. James' data, that people that said maybe they
3 only took 6 grams a day would still have, in some
4 instances, adduct levels that were as high as
5 somebody who took a 24-gram overdose.

6 So I don't think the dosing information
7 that we get in many cases -- I think in a lot of
8 cases it's very good. In the paper that she
9 showed of the 51 cases, those were cases where we
10 were quite sure that we had a specific 25 grams,
11 50 grams taken. And that's why we selected those
12 51 cases for her to study and get those very nice
13 decay curves.

14 But I think in the majority of cases, we
15 have some information. We know they may or may
16 not have taken two different preparations, but the
17 data is limited. There may be more that are
18 taking multiple preparations. They may be larger
19 doses than we think, even. But to tease out a
20 group that's taking 6 grams or less we've found is
21 pretty hard.

22 DR. JAMES: I just wanted to provide an

1 additional comment to the earlier question about
2 whether or not we thought these adducts were real
3 in the setting of toxicity, and just go back and
4 review the early data that we reported in the
5 mouse model.

6 The adduct formation is a dose-dependent
7 phenomenon. And adducts are formed as a result of
8 oxidation of acetaminophen. So what we believe
9 that we are seeing are adducts in liver failure
10 cases that are highly sensitive and highly
11 specific markers of acetaminophen-related liver
12 failure.

13 I think the question gets a lot more
14 difficult when you're talking about therapeutic
15 exposures, and we are just beginning to ask those
16 questions. We have short-term data. We have data
17 from some of Dr. Dart's studies that are
18 short-term. We have data from Dr. Watkins' study
19 that is short-term. And we really don't
20 understand the significance of low levels of
21 adducts in the therapeutic exposure population.
22 But the levels in the acute liver failure

1 population are much higher.

2 I think kind of the -- the other question
3 that was kind of under some of these questions
4 was, if there was a viral infection or if there
5 were another hit and a person took acetaminophen,
6 would they have high levels of adducts? And I
7 think it all goes back to the metabolism of the
8 drug. If that primary hit somehow affected the
9 oxidation of acetaminophen, so affected that
10 primary pathway of metabolism that we know is
11 important in high doses, I think you could say,
12 yes, but I don't think we have those data yet to
13 suggest that a viral infection would alter
14 oxidation.

15 DR. NELSON: Dr. Kerns?

16 DR. KERNS: yes. This question emerged
17 for me when Dr. Budnitz was speaking, so I direct
18 it toward him. With regard to the data on
19 patients that are reporting intentional self-harm
20 and are then described as using combination
21 medications, are there any data, or do you have a
22 qualitative sense, I guess, of whether the people

1 that are found in that situation made an active
2 decision to use a combination medication because
3 of some belief about greater chance of harm, or is
4 it an assumption about -- or an inference about
5 just simple availability of the medication?

6 DR. BUDNITZ: So one point of
7 clarification, if I'm remembering my slides
8 correctly, about half of cases of self-harm
9 attempts involved another non-acetaminophen
10 medication, so two or more separate products. And
11 then another group took combination products.

12 And I don't have any quantitative data to
13 answer your question about what was going on in
14 the minds of the folks who did this in the cases
15 that we have, and unfortunately I cannot give you
16 a good qualitative answer to that, based on the
17 level of detail of the data that we have collected
18 from the ED charts.

19 DR. KERNS: I guess the obvious rationale
20 for my question is there seems to be an
21 inferential leap to thinking that people are
22 making active decisions to selectively use those

1 medications as opposed to it's just simply more
2 available.

3 DR. BUDNITZ: From the data we have, we
4 can't answer that.

5 DR. NELSON: Dr. Levine.

6 DR. LEVINE: I have a question for
7 Dr. Lee. Currently there's a limitation to about
8 three drinks, recommended in the past, of alcohol.
9 I'd like to talk to you about your ideas about the
10 interaction of alcohol with lowering the threshold
11 of acetaminophen overdose.

12 It seems to me that we don't know much
13 about this, and the real question is, how low can
14 you go with alcohol in conjunction with
15 acetaminophen? We do know that, in chronic
16 Hepatitis C and combination therapy treatment, we
17 give Tylenol to our patients, but tell them never
18 to take any alcohol with that. Do we know how low
19 we can go with that interaction?

20 DR. LEE: I don't think the data from the
21 ALF study group can help you. It's observational
22 data. The alcohol quantitation is poor. You

1 saw -- it's about 50 percent are using, but it's
2 often not quantitated. We ask for quantitation,
3 and we get it in some, but the ones that qualify
4 as abuse is in around the 18 percent range.

5 You know the data -- and Dr. Dart talked
6 about it a little bit -- that actually alcohol and
7 acetaminophen compete for 2E1 if you're taking
8 them simultaneously, but in the aftermath of your
9 last drink, you actually do have this heightened
10 metabolism due to induction. But how important
11 that is -- I actually have the feeling that
12 illicit drugs, perhaps the continual buildup of
13 the narcotic dose over several months, or actually
14 drinking to cloud the -- all three of those cloud
15 the sensorium and the judgment and may increase
16 impulsivity.

17 We're actually doing an impulsivity scale
18 when we do this questionnaire. And the scores so
19 far look pretty high, but again, I'm not an expert
20 in this area. I'd have to defer to our psych
21 colleagues for that.

22 I can't help you on exactly what dose

1 should be used.

2 DR. NELSON: Okay. What we're going to
3 do is we'll answer -- we'll have questions till
4 3:00, okay -- if that's okay. And that's about
5 seven minutes from now. So we'll get through as
6 many questions as are on the list that we can
7 until then. And then we'll add those people,
8 again, to the list we had before, if that's okay.

9 Right now, the next person on the list is
10 Dr. Kirsch.

11 DR. KIRSCH: My question is for Dr. Lee
12 as well. So female gender is associated with more
13 liver injury, it appears. And I'm wondering
14 whether there is also an association between
15 female gender and the production of a higher
16 concentration of these toxic adducts.

17 DR. LEE: Not that I'm aware.

18 Dr. James is saying there doesn't seem to
19 be any gender association.

20 DR. KIRSCH: Thank you.

21 DR. NELSON: We like those kind of
22 answers, nice and brief.

1 Dr. Benowitz.

2 DR. BENOWITZ: Another question for
3 Dr. Lee and perhaps Dr. Dart as well. Do you
4 think that narcotic abuse is an issue? You know,
5 you said illicit drugs. But are there some people
6 who are developing toxicity because they are
7 taking Vicodin or Percocet for the narcotic
8 effects?

9 DR. LEE: Yes. I can't quantify exactly
10 how much of that 40 percent group is really
11 building it up, but we clearly have a group that
12 have built up over several months -- typically
13 chronic back pain -- to taking 12 or 15, and seem
14 to have tolerated it. And then, as I say, at the
15 time that they get ill, they have an acute injury,
16 as if somehow they've overcome the threshold.

17 Now, we know from Martin Black's paper
18 that you can build up tolerance to acetaminophen
19 doses, if you gradually increase them, and you can
20 tolerate something that you or I would not
21 tolerate as an acute single overdose. So there is
22 some adaptation to a point, but I think there is a

1 point, probably, where -- either the last day they
2 may take four additional, or they are starving, or
3 they have some other concomitant factor so that
4 they pass a threshold and then develop the
5 toxicity.

6 We're actually also looking at whether
7 there's a plateau effect at the top end; in other
8 words, is there any difference between 20 grams
9 and 50 grams? And we think the answer is no.

10 DR. BENOWITZ: That was not exactly the
11 question, although that's relevant as well. The
12 question is, are there some people, say, who are
13 heroin addicts or primarily narcotics addicts --
14 not taking this for pain, but is this really a
15 drug abuse issue in some cases, where they're
16 using Vicodin because it's cheap and it's a source
17 of narcotics?

18 DR. LEE: I think they start out taking
19 it for pain relief, but become habituated to it,
20 if you will, and gradually crank up the doses, and
21 that's when they're getting two or three different
22 prescriptions at once. But there comes a

1 threshold where they break through and become
2 sick.

3 DR. NELSON: Dr. Dart?

4 DR. DART: There is a surveillance system
5 that's national that does prescription opioids,
6 and it's very clear that there's a substantial
7 proportion -- the number one drug in the drug
8 abuse world is hydrocodone and acetaminophen.

9 Many of the users are aware of it, but
10 they use whatever is available, and so they go
11 shopping, so to speak, among physicians to get
12 those drugs. But it's actually a substantial
13 component. And if you look at those cases that
14 die, then -- it's hard to quantitate it exactly,
15 but a substantial portion of those seem to die a
16 late acidotic liver-type death rather than an
17 early opioid death. But a substantial portion of
18 those, in the poison center data -- because we're
19 using the same data source, except with more
20 detail -- actually die early, very clearly of the
21 respiratory depression portion of it. And then a
22 portion, 25, 30 percent, seem to die from

1 acetaminophen several days later.

2 DR. NELSON: Dr. Chojkier.

3 DR. CHOJKIER: I have a question for also
4 Dr. Lee and Dr. Benowitz perhaps to comment. It's
5 related to the fact that glutathione would
6 prevent -- antagonize the toxic effect of the
7 acetaminophen metabolite, and whether this occurs
8 with a greater frequency and greater -- higher
9 susceptibility among patients with cachexia, they
10 are malnourished, cancer patient, AIDS patient
11 with cachexia -- is something that would be of
12 great interest because those populations use and
13 abuse these types of compounds, and also they
14 would be greatly susceptible.

15 Do you have any evidence that that may be
16 the case?

17 DR. LEE: We don't have good detailed
18 history as to dietary intake on the three days
19 before they came in. I think the only paper is
20 the paper from University of Pittsburgh that
21 suggested that patients were fasting -- were more
22 likely to be fasting when they had hepatotoxicity.

1 DR. NELSON: Okay. Being that it's 3:00,
2 I think we'll move on at this point. The next
3 speaker is Dr. Christina Chang from the Office of
4 Nonprescription Products, to speak about
5 single-ingredient acetaminophen dose-response data
6 in adults.

7 DR. CHANG: Good afternoon. My name is
8 Christina Chang, and I'm a medical officer in the
9 Division of Nonprescription Clinical Evaluation
10 under the Office of Nonprescription Products.

11 In order to provide some background for
12 the committee's deliberation on the option of dose
13 reduction, I'd like to present some information on
14 acetaminophen dose-response data in adults.

15 We know that there is a substantial
16 amount of information supporting the efficacy of
17 acetaminophen at single doses ranging from 325
18 milligrams to 1,000 milligrams, and daily doses up
19 to 4 grams used for a variety of indications. And
20 we've also heard presentations today about the
21 scope of the problem involving
22 acetaminophen-associated liver injury. We're now

1 asking for the committee's guidance in determining
2 the clinical significance of these additional
3 efficacy benefits provided by the current maximum
4 single and daily dose, and therefore I'll focus
5 the efficacy information relating to the advantage
6 conferred by 1,000 milligrams over 650 and 500
7 milligrams acetaminophen given as a single dose.

8 In addition, I will briefly go over the
9 studies investigating the efficacy of
10 acetaminophen in osteoarthritis.

11 I hope to summarize the dose-dependent
12 efficacy information from both NDA files as well
13 as available literature. From the NDA files,
14 there was one new drug application, NDA 17-053,
15 for a 500-milligram acetaminophen capsule that
16 contained data with direct comparison between
17 1,000 and 650 milligrams.

18 A literature search was also performed to
19 identify published reports in which different
20 acetaminophen doses were compared.

21 First to very briefly recap from the
22 regulatory history of acetaminophen from this

1 morning's presentation, acetaminophen belongs to a
2 group of drugs that were introduced into
3 therapeutic use long before the era of
4 well-controlled clinical trials. And the use of
5 acetaminophen dates back to 1893. The approval of
6 the immediate-release dosage strengths began in
7 1950, as I'm showing. By the time the
8 over-the-counter advisory panel was convened in
9 1972, the efficacy of 325 milligrams to
10 650-milligram immediate-release acetaminophen had
11 already been established for single-dose
12 over-the-counter for minor aches and pains.

13 I'd like to present data directly
14 comparing efficacy between 1,000 milligrams and
15 650 milligrams acetaminophen. This information is
16 captured from both the NDA files as well as the
17 literature.

18 I'd like to draw your attention to the
19 only NDA that provided dose-response information.
20 In 1974, the agency approved a 500-milligram
21 capsule formulation for over-the-counter use. The
22 agency requested dose-response data from the

1 sponsor to demonstrate that two 500-milligram
2 capsules would provide additional analgesic
3 benefit relative to two 325-milligram tablets.
4 The approval of this application was based on four
5 efficacy studies in women who got episiotomies
6 during vaginal delivery.

7 The studies were of the same design. All
8 four studies were double-blind randomized
9 placebo-controlled studies in women who got
10 episiotomies. The pain relief was evaluated over
11 four hours after administration.

12 Although there were four studies, only
13 two studies -- that is, studies 1 and 2 --
14 demonstrated statistical superiority of the
15 1,000-milligram dose over the 650-milligram dose.
16 As you can see, study 3 failed to show a
17 difference in dose-response. Study 4 failed to
18 even show separation of active treatments from
19 placebo.

20 The agency approved the application based
21 on the results of studies 1 and 2 which were
22 deemed sufficient to support that a

1 1,000-milligram dose was more effective than
2 650-milligram acetaminophen.

3 The information contained in this
4 application didn't raise any safety concerns at
5 the time and, therefore, the approval was allowed
6 for over-the-counter status for the 500-milligram
7 dosage strength.

8 As to data from literature, there are no
9 studies for fever reduction where direct
10 comparison between 1,000 milligrams and
11 650-milligram acetaminophen was made. That leaves
12 us with the analgesic indication for which there
13 are two reports directly comparing the efficacy
14 between these two doses. The Hopkinson article,
15 as you heard before, used data discussed earlier
16 in the NDA file, and it was reported as a
17 single-dose, double-blind randomized
18 placebo-controlled study, evaluating episiotomy
19 pain over four hours.

20 The authors concluded that
21 1,000-milligram acetaminophen was shown to be
22 superior to 650-milligram acetaminophen in

1 reducing pain intensity as well as providing
2 subjective pain relief.

3 The second study, the Yuan study, was a
4 single-dose, randomized, double-blind cross-over
5 study that used a pain model not used at all for
6 the approval -- over-the-counter conditions. It
7 used a cold-induced pain model. It was conducted
8 by immersing the subject's forearm in ice cold
9 water. The authors reported no differences in
10 efficacy between these two doses.

11 This is a figure taken from Hopkinson,
12 et al., published in 1974, the same year that the
13 500-milligram capsule application was approved.
14 This figure also reflects what was in the
15 application. Three of the studies submitted to
16 the agency were compiled and published in the 1974
17 article. The figure illustrates the intensity of
18 pain over time.

19 In these episiotomy studies, pain was
20 graded using a six-point scale, as illustrated in
21 this figure, from none, to slight, to moderate,
22 moderately severe, severe, to very severe. It's

1 important to note that the mean initial extent of
2 pain was severe for all the treatment arms. The
3 onset of relief from acetaminophen at either dose
4 was fairly rapid, beginning during the first 30
5 minutes following dosing.

6 The efficacy advantage of 1,000
7 milligrams of acetaminophen over the 650-milligram
8 acetaminophen was demonstrated throughout the four
9 hours of evaluation. However, the separation
10 appeared to less than one unit on the pain scale
11 measured.

12 Therefore, to summarize the information
13 on the dose response for the comparison between
14 1,000 and 650 milligrams, the only data showing
15 additional benefit of the 1,000-milligram
16 acetaminophen over the 650 were from two studies
17 submitted to the 500-milligram capsule NDA. And
18 although the same data were included in the
19 Hopkinson article, the publication did not mention
20 that there were two other studies with conflicting
21 results.

22 I'd like to also point out at this time

1 that the data supporting this analgesic benefit of
2 1,000-milligram over 650, they were generated from
3 a very selective group of patients, and that is
4 they're female, usually young and healthy,
5 suffering from severe episiotomy pain. It's
6 unclear if the dose-response findings would be
7 generalizable to mild or moderate pain in the
8 over-the-counter setting.

9 Moving on to comparison data between
10 1,000-milligram and 500-milligram acetaminophen,
11 there is no such information from any of the NDAs
12 and, therefore, the data presented here are from
13 the published literature.

14 In terms of this comparison, there are
15 more consistent data supporting a dose-dependent
16 efficacy. The studies shown on this slide were
17 conducted for the analgesic indication, and these
18 were conducted using validated pain models for
19 over-the-counter painful conditions, and all of
20 them used a 10-centimeter visual analog scale.
21 They were consistent in showing a statistically
22 significant difference, or at least a numerical

1 trend toward the difference between these two
2 doses.

3 However, I should point out that the only
4 placebo-controlled study here was the Seymour
5 study in 1996, but it's the only study in which
6 1,000-milligram acetaminophen failed to show a
7 statistically significant advantage over
8 500-milligram acetaminophen. All the active
9 treatments in the Seymour study resulted in
10 significantly less pain than placebo.

11 The three other studies showing
12 superiority of the 1,000-milligram acetaminophen
13 over 500-milligram were not placebo-controlled.
14 And, in fact, these three non-placebo-controlled
15 studies were excluded from the Cochrane reviews
16 that I'll mention later.

17 There was only one comparison study
18 conducted for antipyresis indication. This is a
19 European study from 2005 that investigated the
20 efficacy, safety and tolerability of aspirin and
21 acetaminophen at 500-milligram and 1,000-milligram
22 doses compared to placebo in adults. All the

1 patients enrolled had acute febrile upper
2 respiratory infection of suspected viral origin.
3 The primary efficacy variable was the area under
4 the curve for the change from baseline in orally
5 measured body temperature until four hours after
6 dosing.

7 The authors were able to demonstrate that
8 both active treatments -- acetaminophen and
9 aspirin -- show dose-related efficacy in fever
10 reduction. As you can see, both the 500-milligram
11 acetaminophen and the 1,000-milligram
12 acetaminophen were effective in reducing body
13 temperature, although 1,000-milligram
14 acetaminophen was more effective.

15 The study also evaluated symptoms
16 associated with viral URIs such as headache,
17 achiness, feverish discomfort, and these were
18 secondary end points in the study. For these
19 parameters, the two doses of acetaminophen
20 performed equally against placebo.

21 Again a quick summary of the information
22 on the dose-response data comparing

1 1,000-milligram and the 500-milligram
2 acetaminophen. In terms of pain relief, all four
3 studies used appropriate pain models for
4 evaluation. There was only one placebo-controlled
5 study out of the four, and it showed no
6 statistically significant difference between 1,000
7 and 500 doses [sic].

8 With respect to fever reduction, both
9 doses were effective. The 1,000-milligram dose
10 did result in a therapeutic advantage of about
11 half a degree Celsius.

12 So given that there was not a substantial
13 amount of data for direct comparisons between
14 different doses, let me turn your attention now to
15 meta-analyses, and specifically the Cochrane
16 systematic reviews, examining efficacy of
17 acetaminophen in post-operative pain.

18 These three reviews included 63
19 randomized, double-blind studies involving
20 thousand of patients. The reviews investigated
21 the efficacy of acetaminophen as well as whether
22 there was an optimal dose of acetaminophen. And I

1 apologize if you have a typo on your printed
2 material. It should say 63.

3 These analyses were conducted based on
4 cross-study comparisons, and that is, the majority
5 of the studies in these reviews didn't directly
6 assess different acetaminophen doses concurrently.
7 The reviews utilized an analgesic concept called
8 the number needed to treat, or NNT. I put the
9 formula for calculation of the NNT up there, but
10 if I need to elaborate later, I'd be happy to.

11 An NNT of 1 is the best possible pain
12 relief. And the higher the NNT values, the lower
13 the efficacy. The NNT measurement, however,
14 though, is not a regulatory end point.

15 With this slide, I'll go over the three
16 analyses in a little more detail. Review number 1
17 was the largest in scope, and it compared
18 single-dose acetaminophen with and without
19 codeine. When compared to placebo,
20 1,000-milligram acetaminophen had an NNT of 4.6.
21 The corresponding NNT for 600 or 650-milligram
22 acetaminophen was 5.3, indicating a lower

1 efficacy. However, the dose-response relationship
2 was not significant because the 95 percent
3 confidence intervals overlapped substantially.

4 The second review focused solely on the
5 dental pain model, included 21 studies which
6 enrolled more than 2,000 patients. There appeared
7 to be a difference between 1,000-milligram
8 acetaminophen and doses under 1,000 in terms of
9 NNT at both four and six-hour time points.
10 However, the review didn't separate out 325, 500
11 or 650-milligram doses of acetaminophen, and it's
12 unclear if the dose-response relationship would
13 still be substantiated had the separation been
14 done.

15 The third review, single-dose oral
16 acetaminophen for post-operative pain was an
17 update of review number 1. It included 47
18 studies, enrolling over 4,000 patients, assessing
19 various post-operative pain in the analyses. And,
20 again, I didn't show the 95 percent confidence
21 intervals for these NNTs, but there, again, was a
22 substantial overlap across all the doses. So the

1 authors concluded that no dose was significantly
2 more effective than any other.

3 To recap from these Cochrane reviews,
4 when data are analyzed using the measurement NNT,
5 acetaminophen is effective for relief of acute
6 post-operative pain at all doses studied.
7 However, the variability of NNTs for different
8 acetaminophen doses were too large to permit --
9 too large to permit a conclusion for a dose
10 response.

11 Now we'll move on to examine data for a
12 maximum recommended dose of 4 grams daily. This
13 dose was established based on the over-the-counter
14 advisory panel's recommendation upon reviewing the
15 data available to the panel up to the 1970s. This
16 daily maximum dose was also reflected in practice
17 guidelines, such as those practiced by the
18 American College of Rheumatology in 2000. The
19 College endorsed acetaminophen as one of the
20 first-line pharmacological therapies in the
21 symptomatic treatment of OA.

22 A comprehensive review on the use of

1 acetaminophen in osteoarthritis was published in a
2 2006 Cochrane review. There were 15 studies. 15
3 trials were included in this analysis. 12 trials
4 used the 4 grams daily maximum and compared
5 acetaminophen with placebo or an NSAID. Of the
6 six placebo-controlled trials, four of them showed
7 that acetaminophen, when given at 4 grams daily,
8 was better than placebo in symptomatic treatment.
9 Overall, acetaminophen was significantly less
10 effective than NSAIDs in providing symptom relief.

11 There were also three trials in which
12 acetaminophen was evaluated at doses under 4 grams
13 per day. One was a placebo-controlled trial --
14 this one -- that showed acetaminophen at 3 grams
15 per day was effective in providing pain relief
16 over seven days.

17 The two other studies compared
18 acetaminophen 3 grams daily with ibuprofen or
19 acetaminophen 2.6 grams daily with Naproxen.
20 While patients treated with acetaminophen at these
21 doses -- they did improve based on pain or
22 functionality end points -- the improvement seen

1 was less than either ibuprofen or Naproxen.

2 So, therefore, to sum up data from
3 osteoarthritis studies in which acetaminophen was
4 evaluated, data supporting the efficacy of 4 grams
5 daily for OA symptom relief are more substantial.
6 However, there is also documented efficacy at 3
7 grams per day as well as 2.6 grams per day.

8 And because there are no studies directly
9 comparing 4 grams daily dose and doses under 4
10 grams, it's unknown how much more analgesic
11 benefit the 4 grams daily dose would provide,
12 relative to the lower daily doses.

13 In summarizing the efficacy data for
14 single-ingredient acetaminophen, I'll just
15 reiterate that the dose-response data are limited.
16 For example, available data differentiating
17 between 1,000 from 650 are limited to severe
18 episiotomy pain, and it's unclear whether this
19 difference would also apply to mild to moderate
20 pain in the over-the-counter setting.

21 The placebo-controlled study comparing
22 1,000 to 500 did not show a benefit of a higher

1 dose. And as for chronic pain due to conditions
2 such as osteoarthritis, there are data
3 demonstrating efficacy from doses lower than 4
4 grams daily. So it's conceivable not all patients
5 with OA will requires 4 grams per day for their
6 symptom relief.

7 And if the higher doses are not
8 significantly more effective than lower doses of
9 acetaminophen for mild to moderate pain, some
10 consumers may be taking amounts more than
11 necessary for their pain relief.

12 I'm not sure if this slide is included in
13 your printed package, so I'll linger a little bit
14 more on this slide. Having discussed the efficacy
15 information on acetaminophen, I would like to draw
16 your attention to the dosing of acetaminophen and
17 contrast that with NSAID dosing.

18 Among the analgesics available
19 over-the-counter, acetaminophen is unique in
20 having the identical daily maximum dose labeled
21 for both Rx and over-the-counter. In contrast
22 NSAID labeling leaves a wider margin of safety for

1 over-the-counter dosing.

2 An OTC consumer whose intake exceeds the
3 maximum recommended doses for these NSAIDs would
4 have some margin of safety before exceeding the
5 maximum recommended Rx dosage, and that's not the
6 case for acetaminophen, as you can see.

7 Finally, I'll remind the committee that
8 the approval of the 1,000-milligram dose of
9 acetaminophen was supported by efficacy
10 information limited to severe episiotomy pain
11 model in the approval at the time. The review did
12 not reveal any substantial safety concerns.

13 And since the original approval,
14 additional safety information has been accumulated
15 on the use of acetaminophen. Specifically, there
16 is concern about the narrow safety margin of
17 acetaminophen with some individuals possibly being
18 at risk at daily doses as low as 5 to 7.5 grams.

19 So perhaps it is time to reassess whether
20 the available efficacy information is sufficient
21 to justify the currently -- current labeled
22 maximum doses in the over-the-counter setting, and

1 that's a risk/benefit calculation that we're
2 looking to the panel for guidance.

3 That concludes my presentation, and I
4 thank you for your attention.

5 DR. NELSON: Thank you.

6 The next speaker is Jane Filie -- I'm
7 sorry if I didn't say that correctly -- from the
8 Division of Analgesia, Anesthesia and Rheumatology
9 Products at FDA, to discuss acetaminophen
10 combination prescription products.

11 DR. FILIE: Good afternoon. My name is
12 Jane Filie, medical officer from the Division of
13 Analgesia, Anesthesia and Rheumatology Products,
14 and I will talk about the prescription
15 acetaminophen combination products.

16 First of all, I will make some remarks
17 regarding the current pain management in the
18 United States and the DEA regulations for the
19 prescription of some drugs used to treat pain. I
20 will also talk about the options available for
21 improving the safe use of acetaminophen
22 combination products and the drug alternatives

1 available for the treatment of pain.

2 Undertreatment of pain is still a major
3 public health issue, with a huge social and
4 economic impact on society. Approximately 50
5 million Americans are partly or totally disabled
6 due to pain. These numbers are expected to rise
7 as the population ages. Usually the treatment of
8 pain begins with non-opioid analgesics, followed
9 by opioid/non-opioid combination analgesics and,
10 ultimately, the single-entity opioid analgesics.

11 Several products are used to treat pain.
12 As already mentioned by Dr. Laura Governale, the
13 combination hydrocodone products have been, by
14 large, the most frequently prescribed analgesics
15 in the past ten years, followed by oxycodone, as
16 single-entity and combination products combined.

17 As shown in this figure, in 2007, there
18 were nearly 120 million prescriptions of
19 hydrocodone combination products. I will now
20 present an overview of the DEA regulations so we
21 can better understand how they affect the
22 prescription of opioid products. The Controlled

1 Substances Act was enacted in 1970 and provides
2 the Drug Enforcement Administration, or DEA, with
3 authority to regulate the manufacture and
4 distribution of narcotics and other products.

5 The Controlled Substances Act lists the
6 controlled substances in five schedules, I through
7 V. The drugs in schedule I are the ones with the
8 highest abuse potential, and ones in schedule V
9 are the ones with the least abuse potential. Only
10 the drugs in schedules II to V are approved for
11 medical use, and I will focus on the drugs in
12 schedules II and III.

13 Among the schedule III drugs are the
14 codeine and hydrocodone combinations. Because
15 these drugs have less potential for abuse than the
16 drugs in schedule II, the distribution
17 requirements are less stringent. These drugs may
18 be dispensed with written or oral prescription,
19 and they may be refilled up to six months after
20 the date of prescription, or refilled up to five
21 times after the date of prescription.

22 These dispensing rules are less

1 burdensome than the ones for schedule II for
2 patients and practitioners in that fewer office
3 visits are required to obtain prescriptions,
4 prescriptions may be called in to the pharmacy,
5 and refills are allowed.

6 Examples of commonly used drugs that are
7 listed under schedule II include the single agents
8 codeine, fentanyl, morphine and oxycodone. These
9 drugs have a high potential for abuse. Because
10 they are schedule II, these drugs have more
11 restricted distribution as they require a written
12 prescription and may not be refilled, which means
13 the patient must provide a prescription to the
14 pharmacy each month. The prescriber cannot write
15 for refills or call the prescription to the
16 pharmacy.

17 Note that hydrocodone alone is a
18 schedule II drug. It is not currently available
19 as a single agent, but if it were, it would
20 subject to these prescribing restrictions.

21 This is a list of some of the combination
22 prescription products containing acetaminophen.

1 Next I will talk about the following
2 options to improve the safety of the prescription
3 acetaminophen products, which are unit-of-use
4 packaging, improving the prominence of
5 "acetaminophen" on the label, medication guide,
6 lowering the dose in combinations and
7 discontinuing narcotic/acetaminophen combinations.

8 Unit-of-use packaging means that the
9 product is packed by industry and shipped to the
10 pharmacy ready for sale without having to be
11 repackaged. This would not necessarily restrict
12 the number of dosage units available in the
13 container.

14 The unit-of-use packaging would improve
15 the safe use of acetaminophen products by allowing
16 the implementation of several measures
17 concomitantly, such as providing standardized
18 information on the package insert, such as
19 warnings and description of active ingredients.
20 For example, all packages would display
21 "acetaminophen" instead of "APAP" and, this way,
22 the name of the ingredient, acetaminophen, would

1 be displayed on all container labels for
2 consistency and clarity.

3 The measure would also allow the FDA to
4 provide risk information through a med guide that
5 would be delivered more consistently as it can be
6 attached to the container.

7 When products are repackaged in the
8 pharmacy, ingredient names can be abbreviated.
9 The unit-of-use packaging would enable the FDA to
10 implement consistent use of acetaminophen on all
11 the labels.

12 Another option is the issuance of a
13 medication guide, or med guide. According to 21
14 CFR part 208. the medication guide is patient
15 labeling for human prescription drug products that
16 the FDA determines pose a serious and significant
17 public health concern requiring distribution of
18 FDA-approved patient information.

19 With repackaging of medications, the
20 delivery of med guides is not always consistent
21 and can be challenging. By implementing the
22 unit-of-dose [sic] packaging, the delivery of a

1 med guide can be improved. However, a challenge
2 remains in terms of ensuring that the patients
3 read and understand the information.

4 Currently, the range of acetaminophen in
5 the combination products extends from 250 to 750
6 milligrams, with the 500 milligrams as the most
7 common amount in prescribed combinations, as
8 previously presented by Dr. Governale.

9 There is little data to support the
10 benefit of a dose of 650 milligrams of
11 acetaminophen over 1,000 milligrams in
12 prescription combination products. Therefore,
13 reducing the amount of acetaminophen in the
14 combination products could help reduce the risk of
15 unintentional acetaminophen overdose.

16 Another option would be the
17 discontinuation of the opioid combination
18 products. Less than half of the cases of acute
19 liver failure have been associated with
20 acetaminophen combination products. On the other
21 hand, one must consider the overall risk and
22 benefit of the alternatives that will replace

acetaminophen/opioid combination products.

Usually, patients who need the combination acetaminophen and opioid drugs may obtain inadequate relief with NSAIDs or may be unable to tolerate them. In addition, patients who are prescribed the combination products are usually deemed not to need single-agent opioids by their prescribers.

I would like to emphasize that hydrocodone is not available as an approved single agent, and its approval would require submission and review of a new drug application. In addition, hydrocodone alone is a schedule II drug which has more restrictions for prescribers and patients. Also, it's important to note that removal of opioid/acetaminophen combination products from the market requires a notice of opportunity for hearing. This provides an individual or company the opportunity for a hearing on a regulatory action before a presiding officer designated by the commissioner.

We can look at the most common diagnoses

1 associated with the use of the most commonly
2 prescribed NSAIDs, the opioid/acetaminophen
3 combinations, and the single-entity oxycodone and
4 hydromorphone. This information is courtesy of
5 Dr. Governale, and what we see is that the
6 diseases of the musculoskeletal system and
7 connective tissue and fractures, sprains,
8 contusions and injuries were the predominant
9 diagnostic codes based on this database for all
10 these products.

11 Among the NSAIDs are the nonselective and
12 COX-2 selective inhibitors. These drugs can cause
13 many adverse effects, as shown. The main concerns
14 are the incidence of gastric ulcers and
15 cardiovascular effects.

16 here I would like to show that in 2008
17 there were 58 million prescriptions for four of
18 the most commonly prescribed NSAIDs in the United
19 States, in contrast to the 120 million
20 prescriptions for hydrocodone products. This does
21 not factor in differences in the amount of product
22 dispensed with each prescription, or OTC use of

1 NSAIDs. However, it does show that were a portion
2 of hydrocodone prescriptions switched for NSAIDs,
3 the number of NSAID prescriptions could increase
4 substantially.

5 NSAIDs are effective and well-tolerated
6 by many. However, the estimated number of yearly
7 hospitalizations for serious GI complications
8 varies from 32,000 per year, according to the FDA
9 acetaminophen working group report, up to 100,000,
10 which is probably on your handouts. And some
11 authors have estimated higher numbers.

12 The estimated number of deaths is
13 estimated to be 3200 or more, as the numbers in
14 the literature also vary. This data suggests that
15 switching any portion of the acetaminophen/opioid
16 combination prescriptions to NSAIDs would not
17 result in an overall reduction in mortality
18 associated with acetaminophen combination
19 products.

20 Other pharmacological options for the
21 treatment of pain belong to the group of opioid
22 agents. These are some of the most commonly used

1 opioids, and they are schedule II, with a
2 substantial abuse potential and restricted
3 prescribing rules.

4 The adverse effects of the opioid agents
5 are well known and are listed in this slide. The
6 main concern with this class of drugs is the
7 occurrence of respiratory depression, addiction,
8 misuse and abuse.

9 This figure presents the retail
10 prescriptions for three opioids dispensed from
11 2004 to 2006, and I would like you to focus on
12 hydrocodone, which is in combination with
13 acetaminophen, and oxycodone, which represents
14 both single-entity and combination products.

15 The number of prescriptions for the
16 hydrocodone products is approximately three-fold
17 higher than the second most prescribed opioid drug
18 for pain, which is oxycodone.

19 Now, this slide depicts major concerns
20 with the use of schedule II opioids which are
21 misused and abused. This is data from the Drug
22 Abuse Warning Network, or DAWN, for 2004 through

1 2006 showing the number of emergency department
2 visits for non-medical reasons, which is one
3 method for assessing misuse and abuse.

4 This database provides information from
5 general hospitals that operate emergency
6 departments. Based on data from sampled units,
7 national estimates of drug-related emergency room
8 visits for the United States are produced
9 annually.

10 While we saw that hydrocodone is the most
11 widely prescribed opioid, what we note here is
12 that there are proportionately fewer emergency
13 room visits compared with oxycodone.

14 It's unclear why hydrocodone products are
15 reported less frequently in the DAWN data.
16 Plausible hypotheses are that the amount of
17 hydrocodone in the combination products, which is
18 limited in order to remain under schedule III, is
19 less likely to result in adverse events severe
20 enough to warrant an emergency department visit.
21 Another hypothesis is that the presence of
22 acetaminophen may have an effect of limiting the

1 intake of the combination drug by misusers. The
2 substitution of the single-entity schedule II
3 opioids for acetaminophen/hydrocodone combination
4 products could result in a rise in cases of misuse
5 and abuse.

6 In summary, the acetaminophen/hydrocodone
7 combination products are the most widely
8 prescribed drugs for the treatment of pain.
9 Improved safety of the combination products may be
10 achieved with improved labeling, patient
11 information, and limiting the amount of
12 acetaminophen in combination products.

13 The elimination of
14 acetaminophen/hydrocodone combination products may
15 not necessarily result in an overall reduction in
16 risk, due to the risks associated with available
17 analgesic alternatives.

18 This concludes my presentation. Thank
19 you for your attention.

20 DR. NELSON: Thank you.

21 It's time to take a break. We've
22 scheduled 15 minutes. I'm going to try my best to

1 keep it to 10. I would ask in the room if anybody
2 that's scheduled to participate in the open public
3 forum has a time constraint -- we're about half an
4 hour behind. If we could push that off about half
5 an hour, we'll be able to keep on track through
6 the agenda. If you have a time restraint, please
7 let Laurie or John at the front desk know, and
8 we'll try to see what we can do about that.

9 Otherwise, we'll be back in about ten
10 minutes, and I'd like to remind the committee
11 again not to discuss pertinent items of this
12 meeting.

13 (A recess was taken.)

14 DR. NELSON: Our next speaker is Ellen
15 Frank of the Division of Public Affairs at the
16 Center for Drug Evaluation and Research regarding
17 the safe use of acetaminophen.

18 MS. FRANK: Good afternoon. My name is
19 Ellen Frank. I'm the director of the Division of
20 Public Affairs in the Office of Communication at
21 CDER, and I'm going to be speaking to you today
22 about FDA's communication program. I'm going to

1 be talking about our outreach efforts on the safe
2 use of acetaminophen for consumers.

3 I'm going to talk a little bit about the
4 history of where we came from, and then I want to
5 show you some of the products we've developed, and
6 then I want to talk about some partnerships that
7 we've been involved with, and then discuss some of
8 the current things that we're doing in looking
9 toward the future.

10 After the 2002 advisory committee
11 meeting, it was recommended that FDA do some
12 education for consumers about the safe use of
13 acetaminophen. So we began a campaign back in
14 about 2004. And this campaign didn't just focus
15 on acetaminophen. We also looked at educating
16 consumers about the safe use of NSAIDs as well.
17 So our messages were both, use acetaminophen and
18 NSAIDs safely.

19 In about 2004, we kicked off our
20 campaign, and we developed a series of products
21 that we then went out with to the public. We had
22 a brochure -- and I'll be showing you some of

1 these as we proceed -- print public service
2 announcements, a consumer FDA magazine article,
3 Internet banners, newspaper articles, and we also
4 did a video.

5 This is an example of the brochure that
6 we developed. We did it in both English and
7 Spanish. And our goal was to get this brochure
8 into the hands of consumers. But it wasn't an
9 easy task because we didn't have funding to
10 produce thousands and thousands of copies. I
11 think we produced about 50,000 or 100,000 copies.
12 But we wanted this to get into pharmacies so
13 consumers could get it at the point of purchase.

14 We met with a lot of the heads of the
15 directors of pharmacies at the major chains, but
16 there wasn't a whole lot of interest in putting
17 this on the shelves. So we do have this
18 available, and we have, over the last four years,
19 had folks ordering this, and they're still
20 available, and it's still a good message, and
21 we're getting these brochures out currently.

22 We developed two public service

1 announcements in 2004. One was focusing on
2 acetaminophen and the other on NSAIDs. But,
3 again, we didn't have funding to pay to put these
4 announcements in magazines, so we were relying on
5 public service space. And it was -- we sent it
6 out, but it's often hard to know who actually
7 picked it up and used it. We hope that there was
8 use, but it's hard -- it was hard for us to tell
9 just how much use these got.

10 We had an FDA consumer article -- and
11 this went out to about 2 -- I think about 200,000
12 subscribers to the FDA consumer magazine. We
13 developed a newspaper article that went out to
14 about 10,000 gazette-type local newspapers
15 throughout the country. We were able to get
16 feedback on placement of this, and how many people
17 might have seen it.

18 We did a leaflet that -- when you pick up
19 your prescriptions at the pharmacy, the little
20 information sheet that's stapled to your
21 prescription, we were able to get remnant space on
22 that and get this message out to consumers through

1 that method.

2 We developed Internet banners in hopes
3 that major websites that had health information
4 would use our banners. These banners directed
5 consumers to our website where they can get
6 additional information. This is an example of how
7 the May Clinic used our banner.

8 And we did a patient safety news video.
9 I'm going to show you a little bit of it, but
10 since this was done in the past and I have some
11 newer versions to show you at the end of my
12 presentation, I'll only show you a little bit.

13 (Video clip played.)

14 MS. FRANK: This was done in 2004, and we
15 have some newer ones that I'll show you at the end
16 of my presentation. We also did a radio
17 announcement that went out to radio stations
18 throughout the country -- I'll show you what that
19 sounded like.

20 (Audio clip played.)

21 MS. FRANK: In 2007, we did another
22 dissemination of a newspaper article, reaching

1 10,000 local newspapers.

2 We have a program called "Medicines in My
3 Home," and the goal of this is to educate
4 elementary school children about how to use
5 medicines safely, specifically how do make sure
6 that they're not taking too much of the same
7 active ingredient. We figured, let's get them
8 while they're young.

9 We had a series of partnerships, and the
10 good thing about this is we, at FDA, can't do it
11 along, and there's a lot of organizations that had
12 the same message that we had, so we joined forces
13 and worked on developing messages together using
14 both our dissemination channels and the partners'
15 dissemination channels. And this worked very
16 well. United Health, National Council on Patient
17 Information and Education, National Consumers
18 League, Wellmark, New York State all work with us
19 in developing materials. Let me show you a few of
20 them.

21 This was a National Consumers League
22 partnership with us. "Don't take me with him;

1 don't take me with him" -- a message of not taking
2 two medications that had the same active
3 ingredient. This public service ad did get a lot
4 of play in magazines.

5 We worked with the NCPIE, National
6 Council on Patient Information and Education, and
7 in 2005 we did a real good media blitz where we
8 reached radio stations throughout the country --
9 this ad went in magazines. There was a video that
10 appeared on TV to accompany this. And, again, the
11 message: Make sure you know what's in your
12 medicine.

13 The United Health Foundation and FDA
14 joined together, and we worked on this print PSA.
15 Came together on the message. And with the help
16 of United Health's over \$10 million worth of
17 funding, we were able to get this message into all
18 of those magazines on the left, something we at
19 FDA could not do on our own.

20 Now, bringing you up to date as to what
21 we're looking at doing now, we're going to
22 continue using the brochure that you saw earlier

1 in my presentation. The message in there focuses
2 on acetaminophen and NSAIDs, but the information
3 is still good.

4 We're going to upgrade the Medicines in
5 My Home program to make an interactive web
6 program. We have Q&As that are going to be on our
7 website. We're going to podcast those Q&As.
8 We're going to make them into a consumer FDA
9 article.

10 And I'm going to show you in a minute our
11 latest videos, one for consumers and one for
12 healthcare professionals. We have fact sheets
13 that are going through clearance, and we divided
14 our fact sheets into specific audiences because we
15 felt the messages -- we can tweak them a little
16 depending on the audience we're trying to reach.

17 Posters that we'd like to get up in
18 pharmacies, clinics, doctors' offices. An
19 in-store announcement -- when you go into your
20 pharmacy and you hear that announcement over the
21 loudspeaker, we're hoping to reach about 5,000
22 pharmacies with a message about making sure that

1 consumers know to use acetaminophen safely.

2 And, again radio and public service ads
3 that we're going to be disseminating throughout
4 the country. Another newspaper article.

5 What we feel is that -- we want to take a
6 multi-prong approach. If we can reach people
7 through a variety of mediums, that's our best --
8 it's the best chance we have to get the message
9 out.

10 I'm going to go ahead and play the two
11 videos that we recently produced. Now, these
12 videos are going out on the web. They also have a
13 podcast that's going to be aired on iTunes. They
14 go on YouTube. There's 200,00 subscribers that we
15 notified that these videos are available. And we
16 also have 100 partner organizations that can use
17 these videos. And we're hoping to get further
18 organizations and partners to use our education
19 materials.

20 I'll show you the videos.

21 (Video clip played.)

22 MS. FRANK: And the next video.

1 (Video clip played.)

2 MS. FRANK: The difference in what we're
3 doing now versus what we've done in the past is
4 that, in the past, a lot of our education
5 materials were focused on educating consumers
6 about being careful not to take too much of the
7 same active ingredient, where now we're
8 specifically telling them, don't take too much
9 acetaminophen. So our message is more direct,
10 more specific and stronger.

11 And we will continue to educate on NSAIDs
12 as well, but our emphasis is going to be on making
13 a strong message to consumers about using
14 acetaminophen safely.

15 These are our websites, and all of our
16 information that you've seen is available and in
17 the public domain, and we encourage everyone to
18 take that information and disseminate it further.
19 Thank you.

20 DR. NELSON: Thank you.

21 Our next speaker is Dr. Laura Shay from
22 the Office of Nonprescription Drugs to discuss

1 over-the-counter use behaviors.

2 DR. SHAY: Good afternoon. Last
3 presentation, although I think there's one more --
4 I don't mean to be saying that to you, Ruth, but I
5 know it's been a long day.

6 What I'm going to try to do is shed some
7 light on the comprehension and behavioral factors
8 associated with OTC medication misuse. Now, in
9 the interest of time, I was going to start the
10 presentation with a fictitious example case, but I
11 think at this point we've all come to terms with
12 knowing that this is a very multi-faceted problem
13 with many areas -- there can be error. So in the
14 interest of time, your slides have some arrow, and
15 I'm going to skip forward to my outline.

16 Al. So I'm going to go into further
17 detail in areas where there is potential for
18 error. I'll first describe survey data on
19 consumer knowledge about products containing
20 acetaminophen and liver warnings, and possible
21 factors associated with OTC medication misuse.
22 First I'm going to describe the data on the

1 consumer knowledge about products containing
2 acetaminophen and the liver warnings.

3 So there was a study conducted by Stumpf,
4 et al., in 2007 on a convenience sample of adult
5 clinic patients. This study actually was
6 conducted in December of 2003. The objective was
7 to determine of the voluntary label revisions for
8 acetaminophen-containing products following the
9 2002 advisory committee meeting had any impact on
10 consumer knowledge about acetaminophen.

11 The voluntary label changes included
12 highlighting active ingredients and the new liver
13 warnings about dangers of higher doses. Now, it's
14 important to note the timing of this survey which
15 was done in December of 2003. At this time, the
16 market would have been in transition, so it's
17 really unknown how many of the participants had
18 actually seen the label changes.

19 A similar study was conducted by Chen,
20 Schneider and Wax in 2002 -- I'm sorry. It was
21 published in 2002, but it was conducted in 2000.
22 The objective of this study was very similar. It

1 was to evaluate knowledge about acetaminophen.
2 This study was conducted prior to the voluntary
3 changes to the label. At this time, the only
4 liver warning would have been the alcohol warning
5 which I have listed here.

6 The study designs were very similar. In
7 both studies the participants were asked to choose
8 from a list of products which products contain
9 acetaminophen, and to choose from a list of
10 problems which ones are associated with taking too
11 much acetaminophen. Both studies did have
12 limitations. In both surveys, an "I don't know"
13 option was not included in the list of products
14 which contain acetaminophen. Therefore, it's
15 unknown how many of the responses were due to
16 guessing. And in the Stumpf survey, two question
17 that -- before they were asked how many products
18 contain acetaminophen, two questions actually
19 stated that Tylenol is acetaminophen.

20 The results of both surveys were very
21 similar. When asked what drugs contained
22 acetaminophen, few chose the acetaminophen/opioid

1 combinations. It's important to also know in this
2 situation it's unknown if any of the participants
3 had actually been prescribed an
4 acetaminophen/opioid combination, and if they had
5 been prescribed one of these combinations, whether
6 or not it actually would have contained the word
7 "acetaminophen" on the label.

8 Several of the participants chose OTC
9 products without acetaminophen, such as Motrin,
10 Advil and Aleve. And in the Stumpf survey -- and,
11 actually, it's interesting. I think the Stumpf
12 survey is what was in that last video because this
13 is the exact report. In the Stumpf survey, the
14 respondents noted that -- 71 percent of the
15 respondents knew that Tylenol contained
16 acetaminophen. However, remember, that means that
17 30 percent, even though they were told in two
18 prior questions that Tylenol is acetaminophen, did
19 not know that Tylenol was acetaminophen. And then
20 50 percent did not know that Tylenol P.M.
21 contained acetaminophen.

22 Unfortunately, Chen's survey did not
23 ask -- did not have Tylenol in their product list.

24 Only 15 percent were aware that the
25 acronym APAP was associated with acetaminophen in
26 the Chen survey. APAP was not one of the products
27 in the list for the Stumpf survey.

28 And only the Chen survey asked what

1 chemical substances are related to the toxicity
2 from a list, where 73 percent selected alcohol.

3 And as far as what problems were
4 associated with taking too much acetaminophen, in
5 the Chen, Schneider and Wax survey, 49 percent
6 reported liver problems, and in the Stumpf survey
7 43 percent reported liver problems.

8 A study conducted by Osborne and Bryant
9 was conducted to assess discharge education for
10 patients prescribed acetaminophen/opioid
11 combinations. This was a retrospective chart
12 review of 108 patients over 18 days of emergency
13 room visits who were discharged on
14 acetaminophen/opioid combinations.

15 When they did the retrospective chart
16 review, they found that no patients were

1 discharged with written instructions to reduce or
2 discontinue use of other acetaminophen-containing
3 medications. And because this was a retrospective
4 chart review, it's unknown whether or not patients
5 did receive any verbal instructions.

6 The remaining slides are an overview of
7 other possible factors that contribute to OTC
8 medication misuse.

9 As seen on the surveys that I just
10 presented on acetaminophen, consumers appear to
11 have limited knowledge about active ingredients.
12 This was also seen in the survey done by the
13 National Council on Patient Information and
14 Education -- or NCPIE survey in 2002 where 66
15 percent reported not buying an OTC medication
16 based on active ingredient, and 66 percent who
17 took an OTC medication for their headache could
18 not correctly identify the active ingredient.

19 So why don't consumers know the active
20 ingredients? One of the reasons may be because
21 some consumers don't read the OTC label. In
22 surveys that questioned participants about OTC

1 medication use, the percentage that report that
2 they don't read some or all of the label is
3 between 5 and 32 percent. It is not known if
4 these percentages are due to social
5 desirability -- which means that the participant
6 actually responds in a way that they think the
7 interviewer wants to hear, which is often a
8 problem with these types of surveys.

9 In the survey done by Chen, Schneider and
10 Wax specific to acetaminophen, they found that,
11 when it came to acetaminophen/Tylenol labels,
12 the -- 45 percent of the participants reported
13 that they never read the label regarding maximum
14 daily dose or side effects. Unfortunately, the
15 reason some consumers don't read OTC labels is not
16 known from these surveys because the questions
17 were not asked.

18 These two surveys were conducted on a
19 convenience sample of general population. the
20 NCPIE survey found that some consumers believed
21 that -- 41 percent of the participants believed
22 that OTC medications are too weak to cause any

1 problems.

2 In a study done by Cham, et al., in 2002,
3 they found that 42 percent did not believe that
4 OTC pain relievers could have side effects when
5 combined with other medications.

6 A study that was conducted in 2005 found
7 that 16 percent believed most OTC medications do
8 not have side effects. This percentage is much
9 lower than the other surveys. However, we cannot
10 conclude that this is a new trend because, unlike
11 the other surveys, close to a quarter of the
12 sample were in training to become home health
13 aides and, therefore, they may have been more
14 educated about medication use.

15 A number of surveys suggest that
16 patients -- I keep saying patients -- consumers
17 take more than directed on the label. When
18 participants were asked if they take more than
19 directed, between 22 to 57 percent report yes.

20 In the NCPIC study, participants were
21 asked why they take more than directed. 68
22 percent reported that they had severe symptoms, 64

1 percent because they did not get better taking the
2 recommended dose; 38 percent had taken the
3 prescription version of the medication before, and
4 29 percent believed that it would bring more
5 relief more quickly.

6 There are a number of studies that have
7 looked at dosing errors in children. The primary
8 causes are difficulty understanding the directions
9 on the label and measuring device errors.

10 For the measuring device errors, there
11 appears to be a higher error rate with dosing
12 cups. Two common errors seen with dosing cups is
13 confusion of the teaspoon and tablespoon on the
14 cup's markings, and the assumption that a full cup
15 is a dose.

16 Accuracy appears to be improved with oral
17 dosing syringes. And with oral dosing syringes,
18 when there is an error, it appears to be more due
19 to underdosing than overdosing.

20 This table shows two studies that
21 compared oral dosing syringes versus dosing cups.
22 You can see that those who use an oral dosing

1 syringe did better than those who use a dosing
2 cup.

3 It's not clear why the dosing accuracy
4 was lower, especially with dosing cups in this
5 study by Sobahni, et al., because the designs were
6 similar and the population tested was also
7 similar. There may have been a difference in how
8 the studies defined an accurate measurement. Only
9 the Sobahni study provided that information.

10 There are researchers who are looking at
11 new innovative ways to present dosing directions.
12 These studies show marked improvement in dosing
13 accuracy with these new methods. The Yin study
14 looked at dosing directions for a liquid
15 prescription medication, and the first study, with
16 an OTC liquid medication.

17 As you can see from the table, the
18 control groups were given standard dosing
19 directions, had much higher rates of overdosing
20 and underdosing than the experimental groups who
21 were given a pictogram-based instruction with
22 teach-back or color-coded dosing instructions.

1 Another cause of incorrect dosing in
2 children has been reported is giving the wrong
3 liquid concentration. The concentration of infant
4 drops is 100 milligrams per milliliter, and for
5 children suspension is 32 milligrams per
6 milliliter. Consumers are often confused as to
7 which product is more concentrated. In the NCPIE
8 survey, 51 percent reported that children's liquid
9 was more concentrated than infant drops. Barrett
10 and Norton had similar findings and provided the
11 following quote from a parent: Children are
12 larger than infants and, therefore, they ought to
13 be more concentrated -- the medicine ought to be
14 more concentrated for the children.

15 Not knowing a liquid's concentration does
16 not in itself lead to incorrect dose as long as
17 the appropriate directions are followed. However,
18 this is a problem when the liquid is not dosed
19 according to a product's directions and is
20 accidentally dosed on directions for a product
21 that has a different concentration.

22 Now, I'm going to touch briefly on

1 regulations for drug advertising. The FDA
2 regulates prescription advertising whereas the
3 Federal Trade Commission, or FTC, regulates OTC
4 advertising.

5 The FTC requires drug claims to be
6 accurate and non-misleading. The FTC does not
7 require a listing of possible side effects or
8 active ingredients.

9 It is estimated that the average American
10 views greater than 30 hours of prescription and
11 non-prescription pharmaceutical advertisements
12 annually. In 2001, there were twice as many OTC
13 advertisements than prescription. Unfortunately,
14 consumer research on the effects of OTC drug
15 advertising on consumer knowledge and perceptions
16 is lacking.

17 This is a page from the May issue of
18 Health magazine. As you can see, there is an
19 acetaminophen ad on the third left of the page
20 next to competing graphics. This ad was written
21 to educate consumers about liver problems that can
22 occur with taking too much acetaminophen -- and I

1 have that listed here.

2 Okay. And this full-print ad was also in
3 the May issue of the Health magazine on the
4 opposite page. This ad does not contain
5 information on possible side effects or the active
6 ingredient. And at the bottom of the page it
7 lists, "Use only as directed."

8 Advertising clearly influences consumer
9 behavior in various ways. Even though the
10 regulations require that OTC labels provide the
11 information needed for safe and effective use of a
12 product, advertisements like this could be viewed
13 as missed opportunity to provide consumers with
14 important safety information.

15 And just of note, this same full-print ad
16 was in the AARP magazine in May/June 2009, again,
17 without the additional information on side effects
18 or active ingredient.

19 So, in summary, unfortunately, the data
20 is limited and many of the studies were conducted
21 over five years ago. However, the data does
22 provide us with some insight into factors that may

1 be causing unintentional misuse of acetaminophen.
2 Many surveyed did not know which products contain
3 acetaminophen or that APAP is acetaminophen. Some
4 surveyed believed that OTC medications do not have
5 side effects, and more than 50 percent surveyed
6 did not know that too much acetaminophen can cause
7 liver damage. There were multiple reasons
8 reported for taking too much OTC medication than
9 directed.

10 Dosing errors in children include
11 difficulty understanding the directions on the
12 label, measuring device errors and confusion about
13 product concentrations. Oral dosing syringes and
14 innovative dosing directions appear to improve
15 accuracy.

16 And, finally, there are opportunities for
17 improvement in relation to healthcare
18 professionals' communication with patients and OTC
19 advertising.

20 That concludes my presentation. Thank
21 you.

22 DR. NELSON: Thank you. We have one

1 extra short talk to insert at this point, given by
2 Dr. Ruth Day of the Medical Cognition Laboratory
3 at Duke University to describe a little bit about
4 I guess insights into human understanding.

5 MS. DAY: My name is Ruth Day and I am
6 the director of the Medical Cognition Laboratory
7 at Duke where we do research on comprehension of
8 drug information -- and this is just a brief
9 snapshot of some of it. It is -- and by the way,
10 there's no handout for this, so I recommend that
11 you watch the screens.

12 The topic is hidden warnings -- hidden
13 warnings for ibuprofen, aspirin and acetaminophen.

14 In our laboratory people come in and we
15 ask them to read the label -- in this case, the
16 Drug Facts label. They have adequate time to do
17 it. And then we test their knowledge of uses,
18 warning and everything else -- warnings,
19 everything else on the label. And, in general,
20 their performance on uses is very good. We test
21 comprehension, memory and other cognitive
22 processes, and in general their knowledge of uses

1 is about 80 percent correct across these tasks,
2 whereas knowledge of warnings is about 20 percent
3 correct on average.

4 So let me just give a brief note about
5 metacognition. Cognition is about what people
6 know; metacognition is about what they think they
7 know. And a lot of these surveys are only looking
8 at metacognition. And there's often a gap between
9 the two. Let me give you one example.

10 So we asked a metacognition question, how
11 easy was it to understand the information in this
12 label? And then people rate on a scale, and they
13 thought it was easy -- easy to very easy.
14 However, they are overestimating their knowledge,
15 as you will see in a moment.

16 So what warnings did we look at? For
17 ibuprofen and aspirin, stomach bleeding, and, for
18 acetaminophen, liver damage.

19 And here's a label for ibuprofen, 2002.
20 I'll blow the part up about warnings, and there it
21 is in its original form. And if you'll take a
22 look, the stomach bleeding is buried at the end of

1 the alcohol warning, if you consume three or more
2 alcoholic drinks every day, ask your doctor
3 whether you should take ibuprofen or other pain
4 relievers, fever reducers. Ibuprofen may cause
5 stomach bleeding.

6 Same thing we've been seeing here today
7 for acetaminophen.

8 So this is the original version, but we
9 did have a couple of enhanced versions. In this
10 next version is pulled out the stomach bleeding
11 warning, put it on a new line and gave it a
12 subtitle. And in another one we kept all of that
13 and then added chunking. Chunking says put
14 together what goes together and separate it from
15 other things. And we separate it in terms of
16 having white space before and after, and other
17 spatial features.

18 On a random basis, people saw and read
19 only one of these, either the original, the next
20 one or the next one, as shown here on the display.
21 What happened?

22 The one with everything, including the

1 chunking, was the best, and as a matter of fact,
2 it was 92 percent improvement in knowing that
3 stomach bleeding was a possible consequence of
4 taking this drug relative to the original.

5 Let's move now to aspirin. And here's a
6 label from 2007 with the Reye's syndrome, allergy
7 alert and so on. And the stomach bleeding is now
8 at the end of the alcohol warning. And we know
9 why it's there. But for the participants it
10 appears to be hidden. Let's take a look.

11 So half of the people got the original
12 version with stomach bleeding hidden, so to speak,
13 at the end of the alcohol warning, whereas in the
14 enhanced version, stomach bleeding had its own
15 chunk and subtitle, just as we saw before. And
16 we're going to plot percent correct, knowing that
17 one of the warnings is stomach bleeding. And
18 there are the results.

19 And as you can see, there's a hundred
20 percent improvement in the enhanced -- with the
21 enhanced version relative to the original.

22 And now we come to acetaminophen. This

1 is one of the P.M. products label we caught in
2 2006. And, again, acetaminophen is at the end of
3 a warning about alcohol. We know why, but the
4 public does not seem to understand this.

5 So now here is one from three days ago --
6 rushed out and got another one. And it's the same
7 thing. Here is the original. And you can see
8 what it looks like. And here is our version of it
9 where we pull it out, the liver warning, say it,
10 and chunk it and so on.

11 We are in the process of collecting data
12 on this, but the data look comparable to what we
13 have seen for ibuprofen and aspirin.

14 So, to conclude, warnings may be
15 physically present, but functionally absent.
16 Physically present we can worry what to say, where
17 to put them, so on and so forth. But they can be
18 functionally absent. If people cannot find,
19 understand, remember or use them, what's the
20 point?

21 As a veteran of the 2002 advisory
22 committee on acetaminophen, I have some experience

1 with recommending that information be put out, but
2 clearly the information is getting across because
3 of the way it's being provided. So that's the bad
4 news. But here's the good news: It's easy to
5 fix.

6 Thank you.

7 DR. NELSON: Thank you.

8 MS. DAY: Can I just comment that there
9 are many cognitive principles that guide how
10 information processing works, and so it's not --
11 and they've been out for over a half a century.
12 So in the new proposed labeling, it applies there
13 as well. Thank you.

14 DR. NELSON: Okay. It is now time to
15 move on to the open public hearing. We're going
16 to come back at the end to the committee questions
17 for speakers.

18 Both the Food and Drug Administration and
19 the public believe in a transparent process for
20 information-gathering and decision-making. To
21 ensure such transparency at the open public
22 hearing session of the advisory committee meeting,

1 FDA believes that it is important to understand
2 the context of an individual's presentation.

3 For this reason, FDA encourages you, the
4 open public hearing speaker, at the beginning of
5 your written or oral statement, to advise the
6 committee of any financial relationship that you
7 may have with the sponsor, its product or, if
8 known, its direct competitors.

9 For example, this financial information
10 may include the sponsor's payment of your travel,
11 lodging or other expenses in connection with your
12 attendance at this meeting.

13 Likewise, FDA encourages you, at the
14 beginning of your statement, to advise the
15 committee if you do not have any such financial
16 relationships.

17 If you choose not to address this issue
18 of financial relationships at the beginning of
19 your statement, it will not preclude you from
20 speaking.

21 The FDA and this committee place great
22 importance in the open public hearing process.

1 The insights and comments provided can help the
2 agency and this committee in their consideration
3 of the issues before them.

4 That said, in many instances and for many
5 topics, there will be a great variety of opinions.
6 One of the goals today is for this open public
7 hearing to be conducted in a fair and open way
8 where every participant is listened to carefully
9 and treated with dignity, courtesy and respect.

10 Therefore, please speak only when
11 recognized by the Chair. Thank you for your
12 cooperation.

13 DR. Davern: I want to thank you for the
14 opportunity to speak and represent the more than
15 3,000 members of the American Association of Liver
16 Disease regarding a passion of mine, and many of
17 members; that is, acetaminophen hepatotoxicity.

18 Our membership is passionate about this
19 important problem because we are at the front
20 lines, caring for patients who suffer from
21 acetaminophen poisoning and ALF on a daily basis.
22 We believe that several decisive steps must be

1 taken by the FDA to reduce the unnecessary and
2 preventible suffering caused by acetaminophen
3 poisoning.

4 Specifically, we can reduce unintentional
5 acetaminophen overdoses through more explicit
6 packaging. We can reduce intentional overdoses
7 through blister packaging and limitations on the
8 number of capsules per purchase.

9 And then, finally, we should unbundle
10 acetaminophen/opiate combinations. I'll focus on
11 the last strategy in my remaining minutes. The
12 data I will present is from the acute liver
13 failure study group which I have actively
14 participated in since its inception in 1998.

15 Based on our data, the incidence of
16 acetaminophen poisoning leading to ALF appear to
17 be increasing over the first six years of the
18 study. As Will Lee may have mentioned -- or did
19 mention earlier, this trend may have flattened
20 out. Nonetheless, acetaminophen poisoning is
21 clearly responsible for the majority of cases of
22 acute liver failure in the U.S., about 50 percent

1 of the total.

2 Is this surprising? Not really. We're
3 surrounded by acetaminophen products, and many of
4 the products are not clearly identifiable as such.
5 Unlike the UK where the vast majority of
6 acetaminophen poisonings are intentional suicide
7 gestures, in the U.S. it appears that roughly half
8 the -- in half the patients with
9 acetaminophen-related ALF, there is no intent of
10 self-harm.

11 Again, data from the acute liver failure
12 study group is instructive here. The really
13 unique feature about the unintentional group, the
14 middle column, is the use of acetaminophen/opiate
15 combinations in over 60 percent. Such compounds
16 are rarely prescribed in the UK, I'm told, and
17 perhaps this explains the relatively rare
18 occurrence of unintentional acetaminophen toxicity
19 there.

20 Well, this begs the question, who came up
21 with the idea of combining a dose-dependent
22 hepatotoxin with a highly addictive drug in a

1 single pill? Furthermore, why is it so much
2 easier to prescribe these drugs than pure opiates?

3 Finally, compounding the problem, these
4 drugs are relatively easy to access over the
5 Internet for patients with relatively little
6 appropriate medical supervision.

7 Given that time is short, let's do a
8 simple calculation, again, using the acute liver
9 failure study database. If 50 percent of cases --
10 of acetaminophen cases are, in fact, unintentional
11 and 60 percent of these are primarily due to
12 acetaminophen/opiate combinations, then do the
13 math. Eliminating these drugs will decrease the
14 incidence of acute liver failure in the United
15 States more than reducing the incidence by
16 eliminating all idiosyncratic hepatotoxins, of
17 which there are dozens. That's the second column
18 there.

19 For perspective, consider the recent
20 decisive FDA actions with regard to Hydroxycut.
21 The FDA received 23 reports of liver problems
22 related to Hydroxycut over an eight-year period,

1 about three a year. The severity varied from
2 asymptomatic elevations of liver tests to
3 transplant and death. There were other problems
4 noted as well, and the FDA recommended removal of
5 Hydroxycut products from the market in April of
6 this year. Three cases per year.

7 We often care for more than three cases
8 of accidental acetaminophen ALF at my transplant
9 center in San Francisco in a busy month.

10 I think we need to keep our eyes on the
11 ball and focus on efforts and our limited
12 resources on strategies to save as many lives as
13 possible. Acetaminophen/opiate combinations are,
14 in my opinion, an ill-conceived idea. It's much
15 analogous to mixing candy and poison, a highly
16 addictive drug with a dose-dependent hepatotoxin.

17 There is no good medical reason that
18 these drugs can't be prescribed separately. Let
19 me repeat that. There is no good reason that
20 these drugs can't be prescribed separately.
21 Patient can be given a prescription for an opiate
22 and a prescription or advice to take

acetaminophen.

Uncoupling acetaminophen/opiate combinations would likely save more lives than all of our efforts to reduce idiosyncratic drug-induced liver injury, including the Drug-induced Liver Injury Network of which I'm a part, and the SAE Consortium, which is partnered with the FDA, as well as other efforts.

I believe regulatory action is needed to uncouple acetaminophen/opiate combinations, and that these drugs should be removed from the market. Unfortunately, I don't think that educational initiatives, whether directed at physicians or at the general population will be effective.

The ASLD and I want to thank you for your time and attention and congratulate you for your efforts in addressing this critically important problem.

DR. NELSON: Thank you. That was Timothy Davern.

The next speaker is Rebecca Burkholder.

1 MS. BURKHOLDER: Burkholder, right, from
2 the National Consumers League. Good afternoon.
3 The National Consumers League is a private,
4 non-profit advocacy group that represents
5 consumers on marketplace and workplace issues.
6 While my presence at this meeting is independent
7 of any sponsor, the league does occasionally
8 receive unrestricted grants from pharmaceutical
9 companies for research and education. We will be
10 sharing with you today some of the findings from
11 NCL commission surveys regarding consumer use of
12 OTC pain relievers with the intent of informing
13 any actions you may take regarding acetaminophen
14 in order to ensure consumer safety.

15 Whatever actions this committee takes,
16 NCL believes it's important to anticipate the
17 resulting consumer response.

18 As you know, and as our survey results
19 confirm, ensuring safe use of OTC medications is a
20 complicated challenge. How do you warn those
21 consumers who are not inclined to read labels?
22 While we don't have all the answers, we do know

1 that consumers need to be reminded that just
2 because a medication is available without a
3 prescription and at their local supermarket, drug
4 store and convenience store, it does not mean that
5 it is risk-free.

6 We know that there is ongoing misuse of
7 OTC pain relievers in America. In a 2003 NCL
8 survey of more than 4,000 adults on their use of
9 OTC pain relievers, including NSAID and
10 acetaminophen products, we found that 44 percent
11 admitted to taking more than the recommended dose,
12 almost half agreed that it is more important to
13 control pain regardless of risk, 50 percent were
14 not concerned about side effects, and only 16
15 percent reported reading the entire product label.

16 As we are looking today at how to address
17 the problem of acetaminophen-related liver injury,
18 we want to share the preliminary top-line results
19 of our recent Harris Interactive Survey of more
20 than 1500 adults and their use and attitude toward
21 OTC and prescription pain relievers, including
22 acetaminophen products.

1 I will focus on the gaps in knowledge,
2 high-risk populations and acetaminophen-specific
3 behavior uncovered by our survey that relate to
4 several of the options that are being considered
5 at this meeting.

6 Generally, we found that almost half of
7 all adults do not know or are not sure of the main
8 active ingredient in the OTC pain medication they
9 take most often. More than half of those who use
10 OTC acetaminophen reported that they are only
11 somewhat or not at all familiar with
12 acetaminophen. 40 percent of acetaminophen users
13 believe it is sold as Motrin. One in six OTC
14 acetaminophen users believe it's okay to take two
15 products containing acetaminophen at the same
16 time. Nearly a third of acetaminophen users said
17 they took their OTC pain medication along with a
18 combination cold or flu OTC medication. And one
19 in six OTC acetaminophen users believe
20 acetaminophen is never combined with other active
21 ingredients in an OTC medication.

22 And, as we just recently heard, consumers

1 don't know that APAP is an abbreviation often used
2 for acetaminophen on prescription drug labels.
3 Only 13 percent have heard or seen the
4 abbreviation and, of those, only 35 percent could
5 correctly identify what it means.

6 We also found populations we believe to
7 be a particular risk for an unintentional overdose
8 based on their responses to our survey. First, an
9 astonishing 47 percent, nearly half of OTC users,
10 have taken a prescription pain medication at the
11 same time as their OTC pain medication. This
12 group of OTC and prescription mixers self-reported
13 engaging in additional risky behaviors and
14 attitudes including half take more of their OTC
15 pain medication than directed, 78 percent -- over
16 three-quarters -- don't usually read the
17 directions on the OTC medication package,
18 one-third don't read the warnings about mixing OTC
19 medications with other drugs.

20 A third of those who mix believe it's
21 okay to take two products containing acetaminophen
22 at the same time. And about one in five of those

1 who mix report that they have trouble
2 understanding a prescription drug label when it
3 comes to the active ingredients and warnings about
4 taking it with other products containing the same
5 ingredient.

6 Another population at risk, based on
7 survey response, is those who take more of their
8 OTC pain medication at a single time than as
9 directed on the label, which is over a third of
10 all adults who use an OTC pain medication. This
11 group reported the following.

12 Two-thirds are not concerned about risk
13 from overdosing. 72 percent report that they
14 don't usually read the directions because they
15 already know how much to take. And 20 percent
16 believe it is not possible to overdose on their
17 OTC pain medication.

18 Now, regarding the options this committee
19 is considering to reduce acetaminophen overdoses,
20 NCL submits the following comments.

21 Reduce current strength of the dose.
22 Since, as our survey reported, many consumers take

1 more acetaminophen pills than directed, reducing
2 the current maximum single adult dose from 1,000
3 milligrams to 625 could potentially prevent
4 unintentional overdoses of OTC acetaminophen.

5 Two, establish package size limits for
6 OTC acetaminophen products. The fact that bottles
7 of 1,000 OTC acetaminophen tablets are readily
8 available to consumers at their local big-box
9 store does not convey that this is a medication
10 that should be used carefully.

11 While establishing reasonable size limits
12 on packages is a step that should be taken, the
13 impact on cost on access, particularly for those
14 consumers who take acetaminophen daily for chronic
15 conditions should be considered.

16 Three, expand product warnings on
17 prescription products containing acetaminophen.
18 As our survey shows, most Americans do not know
19 what APAP stands for. We strongly encourage that
20 the FDA work to ensure that prescription
21 medications containing acetaminophen prominently
22 state the full name, acetaminophen, on the label.

1 Abbreviations are unacceptable.

2 We know from our surveys that some
3 consumers could use help in identifying
4 acetaminophen as an active ingredient in the
5 prescription medications they take.

6 Four, eliminate OTC combination products
7 that contain acetaminophen. We think it's
8 premature at this point to take this action
9 without further research and first trying other
10 interventions to reduce overdoses as a result of
11 taking these products, such as the new FDA label
12 requirements.

13 Consumer response to elimination of these
14 particular OTC combination products could result
15 in increased use of NSAID combination products or
16 in consumers taking it upon themselves to combine
17 products to treat multiple symptoms, both which
18 carry their own risk.

19 Finally, public education. As has been
20 suggested by FDA and others today, we believe that
21 there must be increased public education efforts
22 on the safe use of acetaminophen.

1 This fall NCL will be embarking on an
2 educational campaign on safe use of acetaminophen
3 with particular focus on teenagers and Hispanics.
4 We look forward to working with the FDA on this
5 important issue. Thank you.

6 DR. NELSON: Thank you. The next speaker
7 will be Margalit Ratner.

8 MS. RATNER: My name is Margalit Ratner.
9 I would like to speak about and share with you my
10 experience with Tylenol, how Tylenol really has
11 changed my life.

12 I was a teenager when I had a cold and
13 fever, and the doctor recommended me aspirin.
14 After a terrible reaction of aspirin that caused
15 me hives on my skin, the doctor said that I should
16 not take aspirin anymore.

17 In 1985, I was a single mother raising
18 three children and working a full-time job when I
19 had severe headaches. Because I was allergic to
20 aspirin, I was advised to take Tylenol.

21 In the beginning, I took regular Tylenol
22 and, with time, I changed to Extra Strength. I

1 used acetaminophen for over a decade, but I never
2 took more than recommended doses. In 1997, I
3 began to retain water in my feet. I felt heavier
4 in my body and I wasn't feeling well.

5 After several tests, the doctor found
6 that I was in relatively good health except that
7 my spleen was enlarged and my body was bloated
8 with water.

9 He scheduled me for surgery to see if I
10 have a possible ovarian mass. There was no mass.
11 Then he scheduled me for a liver biopsy since my
12 bilirubin was slightly elevated. But there was no
13 cirrhosis of the liver at that time.

14 I was getting weaker, and I stopped
15 working. I continued to retain water. The doctor
16 tested me for lupus, which I did not have, and I
17 was still taking Tylenol for my headache.

18 In '01/'02, I went to a different doctor.
19 At that time, I couldn't eat, sleep or work, and I
20 was very uncomfortable and cranky. I couldn't
21 breathe. The water was pressing on my lungs. The
22 doctor asked me, what medicine are you taking?

1 And I told him I was taking Tylenol and Lasix.
2 The doctor told me, stop taking Tylenol because it
3 was poisoning -- I was poisoning myself and
4 destroying my liver.

5 At that time, everything was very
6 advanced. It was hard for me to function. The
7 doctor sent me to see a liver specialist in Mount
8 Sinai Hospital in New York City. They said that I
9 would need a liver transplant because I have
10 advanced something like cirrhosis.

11 From that time on, I was more in the
12 hospital than out. They drew fluid with needles
13 every so often to relieve the pressures on my
14 lung. My life was in danger with only 10 percent
15 of expectancy of survival.

16 In '04 I was lucky enough to get a liver
17 transplant. The recovery was a torture.

18 I am here today because I don't want
19 anyone else to go through what I went through. A
20 simple blood test and a warning on the label of
21 acetaminophen not to take if the liver numbers are
22 elevated could save life. Johnson & Johnson is

1 well aware of the effect and the consequences of
2 regular use of Tylenol way before 1985, and
3 definitely in 1997.

4 My transplant was a success, but my life
5 is not the same. I have to take many medication
6 that cause diabetic and other side effects. It is
7 my choice to take these medications and save my
8 life with major side effects. At this time, I did
9 develop diabetic, and my spleen is enlarged and
10 bleeding every so often. I have other medical
11 problems. I am not able to eat many foods or
12 function in a regular routine life without pain.

13 I feel like a beautiful dummy in a store
14 window. I would like to be an asset to the world.
15 Instead, I'm just a burden on everyone. If I can
16 save people's life or help people have more
17 healthier years in their life, then I have
18 accomplished something by coming here.

19 Johnson & Johnson is aware that their
20 product is a danger to some people's liver, and
21 this danger could be very easily avoided.

22 DR. NELSON: Thank you.

1 The next speaker is Dr. Bernard Dreyer.

2 DR. DREYER: Thank you for allowing me to
3 speak on behalf of issues of children. I briefly
4 want to touch on issues of inadequate labeling.
5 Specifically, parents have difficult with OTC
6 labels. We recently did an analysis of the
7 national assessment of adult literacy, looking at
8 parents' responses in which 60 percent of all
9 parents had difficult understanding OTC labels.

10 When you looked at those with lower
11 literacy, which was about 30 percent of parents,
12 74 percent of those had difficulty understanding
13 OTC labels. So that's sort of the beginning of
14 the problem.

15 I also want to touch on measuring
16 devices, on multiple liquid formulations, on
17 combination products and what we don't know.

18 Briefly, I want to first mention that I
19 agree with McNeil request and the FDA request that
20 an instruction should be put on labels for
21 children under two years of age, but I
22 specifically want to focus on evidence that

1 pictogram-based instructions decrease medication
2 administration errors, that standard dosing
3 instruments make a difference, and that not all
4 dosing instruments are equal.

5 This is an RTC that looked at medication
6 instruction sheets that were bilingual, involved
7 plain language and used pictograms, as described
8 here. This is the specific instruction sheet for
9 acetaminophen. There was also a medication log
10 that contained a pictogram that showed the
11 specific dosing for that child. The results of
12 this, if you look at the PRN slide on the left --
13 the red is the control group and the green is the
14 intervention group. And you can see a very
15 significant decrease in medication errors of 24
16 percent due to the pictogram medication
17 intervention.

18 This held up in multivariate analysis,
19 and this shows that both standardized instruments
20 and the medication intervention were important in
21 that those without standardized instruments had
22 2.5 greater odds of error, and those that were in

1 the control group had 5.7 greater odds of error.

2 This is a study that we've done looking
3 at dosing instruments themselves. We asked
4 parents to dose one teaspoonful, or 5 ml with each
5 instrument. A variety of instruments -- you can
6 see -- some dosing cups, oral syringes, et cetera,
7 were used. And in this slide, the brick red are
8 large errors. The yellow are small errors. And
9 the green are no errors. And you can see that
10 both dosing cups had a very significant
11 percentage, about 25 percent of larger errors -- a
12 significant number of small errors compared to
13 other dosing measurements.

14 Looking at this in more detail, these are
15 the two dosing accuracy graphs of the dosing cups.
16 If that is considered acceptable dosing, within 20
17 percent of the dose -- you can see that all of the
18 doses were in the overdose side and not in the
19 underdose side with some significant doses circled
20 there that were more than two times the dose that
21 should have been given. There was about --
22 between 4 and 11 percent of the doses were

1 overdosed in the two times greater than the
2 appropriate dose.

3 In comparison, looking at a dosing
4 syringe, an oral syringe had very few errors, and
5 all errors were less than the recommended dose.

6 These held up in multivariate analyses
7 with very significant adjusted odd ratios for both
8 dosing cups for small errors and larger errors.

9 Finally, I want to briefly comment on the
10 multiple formulations of infant drops and
11 children's liquid, with the infant drops being
12 three times as concentrated. Recently we
13 performed a study to test the hypothesis that this
14 might lead to medication errors.

15 We gave parents a scenario as follows.
16 Your doctor tells you to give Children's Tylenol,
17 and that the right dose for your child is one
18 teaspoon, or 5 ml. You remember that you have
19 acetaminophen at home. When you get home, you
20 look at the box of medicine you have -- and the
21 parent was given an Infant Tylenol drops box.
22 What would you do?

1 And 82 percent of the parents said they
2 would give the infant suspension to the older
3 child. 63 percent used an instrument other than
4 the dropper, with 31 percent giving about 5 mls,
5 approximately a teaspoon. And as you can see,
6 over 40 percent overdosing by greater than two
7 times the dose.

8 This graphically shows those results.
9 You can see that there's the 30 percent of parents
10 giving approximately a teaspoon, between 4 and 6
11 mls. These are parents with greater than 40
12 percent overdosing. And here is parents with
13 greater than two times the overdose.

14 So in summary, we would like to recommend
15 that pictogram-based instruction should be
16 included in OTC liquid preparations. Could be on
17 the box, the bottle, or a separate insert.
18 Specific instructions should be provided for
19 children less than two years of age. Standard
20 dosing instruments should be provided, and further
21 research is needed before determining whether
22 dosing cups should be used, rather than syringes.

1 We would recommend one liquid
2 formulation. We would also recommend that it not
3 be included in combination cold and cough
4 products, and finally that research should include
5 children's issues. Thank you.

6 DR. NELSON: Thank you.

7 The next speaker will be Dr. Kerry Lane.

8 DR. LANE: Good afternoon. My name is
9 Kerry Lane, M.D. I'm a board-certified
10 anesthesiologist. I practice at St. Mary's
11 Medical Center in West Palm Beach, Florida. My
12 topic today is entitled acetaminophen glutathione
13 depletion and regressive autism.

14 Acetaminophen toxicity in the liver is
15 well-established. One of the known toxic effects
16 of this commonly used drug is depletion of the
17 most important antioxidant, glutathione.

18 Disease states that link the depletion of
19 glutathione and excessive amounts of oxidized
20 glutathione versus reduced glutathione include
21 diabetes, atherosclerosis, AIDS, Alzheimer's and
22 pregnancy-induced hypertension. Regressive autism

1 is a condition that has defied a definitive
2 pathobiology to date. The attachments I have
3 enclosed reveal that acetaminophen, by
4 exacerbating an already depleted glutathione
5 antioxidant system due to a pre-existing
6 condition, triggers autism in the peri-vaccination
7 period by reducing glutathione levels to below a
8 critical level.

9 Adequate glutathione levels are crucial
10 to the effective functioning of the
11 metallothionein system. The metallothionein
12 systems is involved in the metabolism of metals,
13 as is glutathione. However, the metallothionein
14 system is especially critical to metabolism of
15 zinc in the brain.

16 In states of depleted glutathione and
17 excess oxidized glutathione, free zinc is released
18 in brain cells. This free zinc is toxic to the
19 mitochondria, causing cellular hypoxia and a
20 generalized neurological malfunctioning that we
21 now recognize as autism.

22 It appears acetaminophen alone is not

1 enough to cause autism. The comorbid pathobiology
2 is due to the creation of a state of abnormal
3 gastrointestinal biology due to antibiotic
4 administration to the infant. This allows the
5 replacement of the normal GI flora with yeast or
6 regrowth by candida species and others. Many
7 yeast and fungi produce microtoxins which have
8 been shown to be pathological to man and animal
9 alike.

10 Recent interest has focused on a
11 microtoxin known as gliotoxin which has been shown
12 to be immunosuppressive by killing CD4 cells along
13 with a multitude of other deleterious effects.
14 Gliotoxin has been shown to form adducts with
15 glutathione, essentially removing it from the pool
16 of bioavailable antioxidants.

17 Over 50 percent of candida species have
18 been shown to produce gliotoxin.

19 If we envision a sequence of events that
20 results in undesirable yeast in the GI tract,
21 causing a depletion of glutathione and generalized
22 oxidative stress, followed by vaccination that

1 includes a metal adjuvant, either mercury or
2 aluminum, followed by the administration of
3 acetaminophen as an antipyretic to an infant at a
4 critical period of neuro development, we can
5 envision the pathobiology of autism.

6 Recent disclosure of the toxicology of
7 free zinc, as evidenced by the loss of taste and
8 smell with the use of the over-the-counter product
9 Zicam, is further evidence of the likely
10 pathobiology of autism I described above.

11 Furthermore, the onset of the autism
12 epidemic in large numbers in the mid-1980s can be
13 directly -- can be explained by the shift away
14 from aspirin as an antipyretic and the
15 substitution of acetaminophen in its place.

16 The instance of Reye's syndrome, thought
17 to be caused by aspirin in the early 1980s, was
18 approximately three cases per million. The
19 incidence of autism today is approaching one in
20 150, a 10,000-fold case occurrence rate increase
21 over the incidence of autism. Clearly, this must
22 not be allowed to continue.

1 The enclosed attachments from
2 peer-reviewed articles are a road map to the
3 above-described pathobiology. I suggest the FDA
4 act with all due haste to make this material
5 public so the autism epidemic can be stopped.
6 Additional focus should be directed towards the
7 AIDS syndrome which also involves depletion of
8 glutathione. It would seem acetaminophen is also
9 inappropriate in this setting. Thank you.

10 DR. NELSON: Thank you.

11 Our next and final speaker is Paul
12 Desjardins.

13 DR. DESJARDINS: Thank you, ladies and
14 gentlemen, for giving me time to speak this
15 afternoon. My name is Paul Desjardins. I'm
16 senior vice president for global clinical and
17 medical affairs at Wyeth Consumer Healthcare, and
18 I'm speaking on behalf of Wyeth Consumer
19 Healthcare this afternoon.

20 As a manufacturer of OTC analgesic
21 combinations that contain both ibuprofen and
22 acetaminophen, we support the agency's review of

1 acetaminophen. While we do not advocate for
2 reducing public access to safe and effective
3 medications, we look forward to working with the
4 agency to improve the safe use of these products.

5 My comments this afternoon will focus on
6 two key points. First, I'll present Wyeth's
7 position on OTC acetaminophen combination
8 products, and second I'll provide comments on the
9 epidemiologic model presented on behalf of McNeil
10 this morning.

11 Wyeth has made a written submission to
12 the docket to elaborate on my comments this
13 afternoon, and that will be available to you in a
14 couple of days, I understand.

15 The FDA working group has recommended
16 removing of all acetaminophen-containing products
17 from the market as one option to minimize the
18 likelihood of unintentional overdoses with such
19 combinations. Wyeth does not support this
20 recommendation. The removal of these products
21 would deprive consumers of valuable therapeutic
22 options, and it represents an extreme approach for

1 addressing the public health concern of
2 intentional and unintentional overdoses with
3 acetaminophen, leading to liver toxicity.

4 The agency's overall public health
5 concern would be better served by an available
6 approach, which we feel has not been adequately
7 discussed this afternoon. We believe the FDA
8 should consider regulating acetaminophen
9 combination products under the new drug
10 application process.

11 The OTC monograph works well, and it is
12 critical to bringing consumers safe and effective
13 OTC products. However, when unique safety signals
14 arise, such as liver toxicity, it is appropriate
15 for FDA to respond in a manner that balances both
16 patient safety with patient access to effective
17 medication.

18 The NDA process allows FDA to take
19 actions based on the safety profile of a
20 particular ingredient and to target corrective
21 actions to a specific product. This would allow
22 for continued OTC availability of combinations,

1 while providing FDA with more dynamic means for
2 pre- and post-marketing oversight and
3 intervention.

4 For example, NDAs give FDA the
5 opportunity to review labeling prior to marketing.
6 Considering that there are approximately -- and
7 we've heard estimates of 250 to 600 products that
8 contain acetaminophen under many different
9 proprietary names -- this would be an effective
10 way to reduce the possibility of medication errors
11 related to either look-alike or sound-alike names,
12 as well as labels or packaging device that may
13 contribute to errors.

14 Unlike OTC acetaminophen combination
15 products, the 16 ibuprofen and Naproxen
16 combinations are already subject to the NDA
17 process. As a result, those manufacturers already
18 provide to the FDA labels for review prior to
19 marketing.

20 The NDA process has several
21 post-marketing advantages as well to deal with
22 acetaminophen liver toxicity. Not only would the

1 agency receive periodic safety reports, which
2 would be the basis for monitoring effects of
3 recommended public health interventions, but FDA
4 would then have the ability to act expeditiously,
5 if those interventions are not as successful as
6 anticipated.

7 To summarize, on the first point, Wyeth
8 believes that acetaminophen combinations are an
9 important OTC treatment option that should
10 continue to be available to consumers. However,
11 the unique public health concerns of
12 acetaminophen-related liver toxicity warrant the
13 closer oversight that an NDA can provide.

14 Now let me turn to the mathematical
15 epidemiologic prediction model presented this
16 morning by Dr. Rothman on behalf of McNeil. The
17 epidemiologic model, which argued that
18 acetaminophen restrictions would lead to switches
19 to NSAIDs and increased GI and renal toxicity has
20 three major flaws.

21 First, it is inappropriate to use
22 relative risk of prescription doses of

1 non-steroidal drugs in a calculation to determine
2 the health impact of increased OTC NSAID use. OTC
3 NSAIDs are generally half the strength of
4 prescription doses, as was presented by a speaker,
5 and are taken for a maximum of ten days.

6 High-dose prescription NSAIDs can be used
7 without limitations on duration of use, which
8 increases the risk of certain side effects.

9 Second, the mathematical models are
10 generally employed for epidemiologic
11 decision-making and hypothesis testing when a
12 public health intervention has never been formally
13 evaluated in a real-world population. In fact,
14 there are observational data from the UK which
15 have been clearly shown -- which have shown that
16 shifting a population away from OTC acetaminophen
17 to OTC ibuprofen consumption does not produce any
18 measurable increase in mortality for GI
19 hemorrhage, peptic ulcers and renal failure.

20 In other words, the real data do not fit
21 the dire predictions we heard this morning.

22 Finally, it's not accurate to use one

1 relative risk number to represent potential side
2 effects for NSAIDs as a class. Each ingredient
3 must be evaluated using its own safety profile.
4 Even the citations used in Dr. Rothman's paper to
5 argue for the model recognize the fact that NSAIDs
6 have different relative risks.

7 In summary, we believe that these major
8 flaws account for the significant difference
9 between what was seen in the UK in real-world case
10 and this morning's predictions.

11 The overall safety of switching patients
12 from OTC acetaminophen to OTC NSAIDs would likely
13 not result in the numbers of serious events
14 predicted by the sponsor's model. And we look
15 forward to hearing the comments tomorrow from
16 experts from the UK. Wyeth also believes that the
17 NDA framework allows for a dynamic and relevant
18 oversight to protect the public health while
19 preserving access to OTC products.

20 Finally, the monograph process has been
21 useful for most OTC products. However, the public
22 health concerns with acetaminophen liver toxicity

1 requires a different solution. Thank you for
2 considering our position in your deliberations.

3 DR. NELSON: Thank you.

4 The open public hearing portion of this
5 meeting has now concluded, and we will no longer
6 take comments from the audience. The committee
7 will now turn its attention to address the task at
8 hand, the careful consideration of the data before
9 the committee as well as the public comments.

10 Okay. So we're back now to the committee
11 questions -- to the speakers, and hopefully
12 they're all still here. Now, I have a list -- and
13 it's not extensive -- of people that want to ask
14 questions. But my goal here is to try to run this
15 till about 5:30 or so. So hopefully we'll get
16 down that list and we'll be done. Others, if they
17 feel like they want to put their name on the list
18 and maybe wait and see if we get them at the end,
19 that's fine.

20 I'm going to go a little bit out of order
21 on our list, in case you know where your name is,
22 because I want to make sure that the people that

1 haven't already made comments are able to actually
2 do so.

3 The other thing, before I forget -- and
4 I'll probably remind you again -- is that there is
5 a change in the schedule for tomorrow. I'm told
6 it's an honest oversight. But we are not starting
7 at 8:30, as it says in the agenda, but we're going
8 to start at 8:00. Okay? And that will hopefully
9 help us ensure that we'll finish on time tomorrow.

10 Okay. So back to the questions. The
11 first question, Dr. Pollock.

12 DR. POLLOCK: This is a question from
13 really early this morning, and it was for
14 Dr. Breitmeyer. Is he still here? Thank you.

15 So my question -- one of the few areas
16 that we seem to have consensus here, or at least
17 some semblance of consensus, is that we -- most
18 people seem to be in favor of dosing guidelines
19 for children under the age of two to be included
20 with whatever pediatric formulation is ultimately
21 available for them.

22 My question for you relates to some of

1 the clearance data that you presented to us today.
2 Based on the data that you presented for children
3 under the age of two, do you think we have enough
4 information now to make appropriate guidelines for
5 children under the age of two?

6 DR. BREITMEYER: Well, I don't think -- I
7 didn't show you our whole model, and the amount of
8 pharmacokinetic data that's in our NDA is
9 substantially more -- it's more extensive than
10 what I showed.

11 I do think that there is enough
12 information there to consider alternate dosing
13 guidelines.

14 For example, a reasonable dose for
15 newborns, from the totality of our data, appears
16 to be in the range of 30 milligrams per kilogram
17 per day, substantially lower than what you would
18 get from the Harriet Lane or PDR algorithms.

19 And so we are willing to share our PK
20 information in a more thorough form. The division
21 has it now. We're expecting to go through
22 discussions with the pharmacokinetic experts at

1 the agency in terms of developing our own dosing
2 guidelines for children, and so are certainly open
3 to sharing the information in a manner that would
4 be helpful to you.

5 DR. NELSON: Dr. Shrank.

6 DR. SHRANK: Thanks. One of the concepts
7 that came up frequently this morning in the
8 industry presentation had to do with the extent to
9 which combination products may reduce risk. And
10 the only evidence that seemed to be presented was
11 a paper by Messerli, and I know that he or she
12 might have been here earlier. And I wondered if
13 you could provide some information clarifying what
14 that data shows.

15 So -- there was just a description that
16 the combination products improve adherence, and I
17 was wondering if you could give more specifics
18 about the kinds of drugs that were included in the
19 studies in this meta-analysis and the kind of
20 outcomes you looked at and what we really know
21 about this topic.

22 DR. SUYDAM: I'm sorry, but Dr. Messerli

1 had to leave. I just saw him walk out about five
2 minutes ago. I think he had a plane to catch.
3 Dr. Silberstein is here. He can talk about the
4 benefits that he sees from his study. He's the
5 one who did the migraine -- the headache
6 combination.

7 DR. SILBERSTEIN: Yeah. Chris Diener in
8 Germany did an article looking at all the
9 different components. We did a paper in this
10 country comparing ibuprofen to acetaminophen,
11 caffeine and aspirin -- another one comparing it
12 to sumatriptan.

13 The way I look at it is essentially the
14 combination analgesics provide better analgesia
15 with a lower dose of each component. So, for
16 example, the combination in the German study
17 showed that 400 milligrams of acetaminophen was
18 less -- was more effective in the combination than
19 1,000 milligrams alone. So, therefore, what
20 you're really getting in the combination products
21 is a dose-sparing effect.

22 Was that useful for you?

1 DR. SHRANK: Well, not entirely. The
2 goal is to find -- there was a meta-analysis or
3 some sort of systematic review or -- I'm not sure
4 what happened, but there was a study that was done
5 that was presented briefly, and I think it would
6 be useful to get a sense of, you know, what kinds
7 of information --

8 DR. SUYDAM: Yes. And that was
9 Dr. Messerli's --

10 DR. SHRANK: Yeah. I know that he's not
11 here.

12 DR. SUYDAM: That was Dr. Messerli's
13 study. I can -- I'm sorry. I'm not as familiar
14 with it. I certainly am not as familiar with it
15 as him.

16 Slide on.

17 Perhaps this might help. This is the --
18 this, I think, shows you that you have better --
19 the combinations actually improve medication
20 compliance over time with a variety of studies,
21 and you can see the number of studies on the left.

22 DR. SHRANK: So I think what would be

1 useful -- so long-term compliance to, like, a
2 chronic medication obviously would be different
3 than appropriate use, or overuse, in the short
4 term of a medication to treat symptoms. And it's
5 not clear what classes of drugs we're looking at
6 here. It's not clear, really, what we're seeing.

7 So considering that this is, you know,
8 one of -- sort of a key topic, or a key concept in
9 this discussion, it seems like it would be useful
10 to get a better flavor for, if there's any
11 evidence to suggest that the fixed dose
12 combinations actually -- so I wouldn't expect
13 long-term compliance or adherence to be an outcome
14 that we really care about.

15 DR. SUYDAM: Okay. Well, we can try to
16 find something else.

17 MS. FERGUSON: Can you please provide
18 your name for the transcriber.

19 DR. SUYDAM: I'm sorry. Linda Suydam,
20 CHPA.

21 MS. FERGUSON: Thank you.

22 DR. NELSON: Dr. Morrato.

1 DR. MORRATO: Thank you. This also is a
2 question that harkens back to earlier this
3 morning. It sounds like there's general consensus
4 on the value of education. And as we heard, you
5 know, ensuring that patients and caregivers are
6 aware of the warning, that they know to use the
7 lowest effective dose.

8 So my questions relate to whether or not
9 the proposed education plans that came from the
10 consumer healthcare products, as well as McNeil --
11 some greater elaboration on whether or not what
12 they're proposing is a sufficient strategy to
13 actually move the bar on knowledge and behavior.

14 So two questions. One is, in light of
15 wanting to have an aggressive educational
16 campaign, can you elaborate a bit more in terms of
17 what is planned in terms of reach and frequently,
18 not just doing it so you can check the box that
19 it's on some PSA or corner of a magazine, but a
20 little bit more elaboration on the scale. And
21 perhaps a bit more elaboration on how there might
22 be coordinated efforts, particularly with what the

1 FDA is doing, so that there's a consistent
2 message.

3 And then the second one relates to
4 evaluation of the education program, that if
5 you've given consideration that there might be
6 teeth or stopping rules in what you're doing in
7 the evaluation. So in light of not seeing
8 sufficient change in knowledge, awareness and
9 behavior, that other action might be taken. So
10 that if the proposal is not to go ahead with
11 eliminating combination products because education
12 can overcome a lot of the issues raised, thinking
13 of success measures so we know if that's
14 happening, and if it's not, that a next step might
15 be elimination.

16 So have you considered a more detailed
17 evaluation?

18 DR. SUYDAM: The answer to that is yes,
19 and we are working with the FDA, and they will be
20 part of the consortium that I presented that will
21 be helping to design the overall program.

22 But I'd like to ask Dr. Saul Shiffman,

1 who is the educational expert, to talk about the
2 nature of these kinds of programs and how they can
3 be evaluated.

4 DR. SHIFFMAN: Let me actually start at
5 the end to your question about evaluation, because
6 I think that's critical. So Dr. Suydam mentioned
7 in passing that the program includes evaluation
8 all along the way. And the important part of that
9 is that we want to know not only is it working in
10 the long run, but the idea is to use quantitative
11 evaluation through frequent surveys of
12 acetaminophen users to ensure that the program is
13 working all along the way and, therefore, use it
14 to adjust the program as we go.

15 So it's very much an empirically-driven
16 kind of strategy, and that's exactly the strategy
17 that's been shown to work in educational programs
18 in other areas.

19 You raised the issue of what do you do
20 about the evaluation, and I've addressed that in
21 part by saying that one of the steps is make sure
22 that you're improving the program if the data are

1 telling you that it's not working.

2 But I think the other element, which
3 Dr. Suydam also mentioned, is that this is
4 intended to be collaborative with FDA. So FDA
5 will know if things are not working and whether
6 further steps are taken.

7 I do want to address the issue of the
8 effectiveness of educational programs because
9 often -- in fact, we heard some about a program
10 that has been mounted, but we didn't see data.
11 And I think it is critically important to have
12 data.

13 Actually, if you can put that slide on.

14 These are just some examples that are
15 documented in the peer-reviewed empirical
16 literature -- and they are just examples; it's not
17 a comprehensive set -- in which data were
18 collected. There were baseline data and there
19 were follow-up data to show that the programs
20 work.

21 And I want to make a very important
22 point -- it's on the title of the slide -- which

1 is that the intention is to change behavior. So
2 obviously the target of an educational campaign is
3 cognitive; we want to change what people believe
4 and think about. But the purpose of that is
5 really to change their behavior.

6 So the focus of the program will be on
7 changing how people use acetaminophen, and the
8 targets that would be tracked in that kind of
9 evaluation would be to see reductions in the kind
10 of end points Dr. Suydam mentioned; that is, less
11 frequent use of more than the recommended dose,
12 less frequent use concomitant with heavy drinking,
13 less frequent use with multiple acetaminophen
14 products.

15 But the point is that it's a data-driven
16 program, and that programs that are not only
17 evaluated, but developed from data have been shown
18 repeatedly to work in changing behavior.

19 DR. MORRATO: So will those plans be
20 publicly shared as well, so there's some
21 transparency?

22 DR. SHIFFMAN: I believe that they will.

1 In fact, what we've talked about as well --
2 because it is hard to find data on this in the
3 peer-reviewed literature -- is getting the results
4 of the program published as well.

5 Now, hopefully you're not going to have
6 to wait to hear from CHPA what the program is,
7 because if it's done effectively, you should see
8 it in your magazines and on the web --

9 DR. MORRATO: Right. So that's -- back
10 to my first question, then, is there discussion as
11 to the scope and the scale of the actual campaign,
12 you know, in terms of --

13 DR. SHIFFMAN: That's very much under
14 discussion. As you've heard, there are a lot of
15 players who are contributing to the campaign and
16 so it has to be sorted out who's going to do what.

17 Part of what -- one of the hallmarks of
18 effective campaigns is that you hit multiple
19 channels so that -- while we've talked a lot about
20 advertising, we think it's very important, for
21 example, for pharmacists to be providing this
22 information to consumers at the point of purchase,

1 for physicians to be providing information at the
2 point of prescribing, particularly if they're
3 prescribing an Rx combination.

4 So the intention is to have very
5 wide-reaching reach, and we're working with
6 partners -- again, I think, including FDA to make
7 sure that that happens. It's not unlike drug
8 development. You have to have an adequate dose to
9 see an effect.

10 DR. MORRATO: Right. And that's what we
11 want to make sure happens.

12 DR. SHIFFMAN: Exactly.

13 DR. MORRATO: And then I'll just say -- I
14 notice that the American Academy of Pediatrics I
15 don't think was on the list, and that would be a
16 good one to include. I saw American Academy of
17 Family Practitioners. So...

18 DR. SUYDAM: We have tried to engage the
19 American Academy of Pediatrics and have yet been
20 able to get them to engage on this to make a
21 decision to join the group.

22 We've actively asked them, and we're

1 still waiting to hear if they're willing to do
2 that. But we agree with you. We would love to
3 have them be a part of it.

4 DR. NELSON: Dr. Engle.

5 DR. ENGLE: My question relates to
6 Dr. Kuffner's presentation this morning, and
7 specifically on slide 47. On that slide he showed
8 some potential new packaging for the concentrated
9 Tylenol drops, and he was talking about flow
10 restrictors.

11 I guess my question is, Tylenol, already
12 in the concentrated drops, has a flow restrictor.
13 It's different than what's shown in this
14 particular slide. But what I wondered is, does
15 McNeil have data to show that that flow restrictor
16 actually made a difference? Because they are one
17 of the few manufacturers that have that.

18 So over the past few years -- because
19 it's been several years since that has been in
20 play -- is there any data to substantiate that
21 that would be a helpful packaging improvement?

22 And then my second question relates to

1 what's depicted in the slide here with the dosing
2 syringe. The current product has the dropper
3 which is attached to the top, and it's part of the
4 product. When you get the dosing syringes,
5 they're separate. And so my question is, do we
6 have any data or any information that relates
7 to -- do parents tend to lose that dosing device,
8 or use something else?

9 We already heard data that said that even
10 with the dropper attached, people will try to use
11 teaspoons. So I just wondered if there was
12 anything that could help us understand whether
13 having a separate device would actually help, or
14 could that actually cause more problems?

15 So those are my questions.

16 DR. KUFFNER: So I'll start by answering
17 the second question first. We don't have specific
18 data in terms of having a separate device,
19 especially a syringe. When it comes to our dosing
20 cup that comes with our Children's Tylenol
21 products, we don't see that there's an issue in
22 terms of a large percentage of consumers or

1 patients or caregivers actually either misplacing
2 the dosing cup -- that really isn't an issue.

3 When it comes to the dosing syringe, we
4 feel -- and you saw some data from Dr. Dreyer that
5 syringes may potentially be more accurate, and
6 that's something that we're looking into. And so
7 we feel the PIBA device has the advantage of
8 preventing the accidental unsupervised ingestions,
9 but then also potentially preventing medication
10 errors, especially since caregivers can only
11 access the medicine with the syringe. And so
12 there wouldn't be any possibility of either
13 pouring or squeezing that medicine out with the
14 PIBA device in there.

15 Your first question goes to, I think, one
16 of the hearts of the issue, is that when we embark
17 on this multi-faceted risk mitigation framework
18 that is going to include packaging and labeling
19 and education, we need to set the baseline and we
20 need to set out and develop clear metrics and
21 understand from the beginning how we're going to
22 collect data.

1 McNeil did put a sort of flow restrictor
2 or a safety lock on our infants' products a number
3 of years ago. As I said, we have seen in recent
4 years that we haven't had cases of hepatotoxicity,
5 either moderate or severe, or fatal cases with the
6 infants' concentrated product since 2004.

7 I can't tell you today that that was a
8 specific reason for it, but that certainly may be.

9 As we move forward and we put these new
10 packaging innovations into place on different
11 products, we are going to establish a baseline so
12 that we truly can measure the effectiveness of the
13 interventions.

14 DR. NELSON: Dr. Raja.

15 DR. RAJA: Srinivasa Raja. This question
16 relates to this afternoon's presentation by
17 Dr. Chang and this morning's presentations by
18 Dr. Cathy Gelotte. Both address an important
19 issue of the differences in efficacy of the 1,000
20 milligrams versus the 650 milligrams of
21 acetaminophen. Both presented data from similar
22 studies, but the conclusions made were very

1 dissimilar.

2 One of the things I observed was the
3 slide presented by Dr. Chang included actual pain
4 intensity scores, while this morning's
5 presentation had pain intensity difference or the
6 responder rate analysis.

7 Could the different conclusions be purely
8 because of different outcome measures, or are
9 there other reasons for these dissimilar
10 conclusions that were made?

11 Maybe Dr. Chang first, and if Dr. Gelotte
12 is available.

13 DR. CHANG: Just looking over the
14 briefing document provided by McNeil, as I
15 described it before, the Hopkinson article really
16 is a compilation of the three studies that have
17 been submitted to the NDA [sic], and only two of
18 them were positive studies.

19 The -- from the briefing document, they
20 presented nine studies comparing 1,000 milligram
21 and 650. Not counting the Yuan study, which was
22 the cold-induced model -- that's not used in
23 OTC -- they have eight studies, and four of them
24 were company data that I didn't have access to.

25 And the four studies that ultimately got
26 published were the Hopkinson, Bare, Posatko and
27 Wallach -- those were the four studies that had
28 been submitted to the agency for review. And so I

1 reached the conclusion based on my review of the
2 NDA data and the published literature.

3 DR. GELOTTE: The approach that we took
4 this morning was to answer the question, what
5 would be the increased benefit of looking at the
6 650 dose to 1,000, and also to 500. In doing
7 that, we looked at the individual studies -- and
8 as Dr. Chang has pointed out, we had located in
9 our database from the 1980s a few dental pain
10 studies that we had conducted.

11 Now, what we wanted to do is answer the
12 question, how much or what greater proportion of
13 subjects would attain at least 50 percent of the
14 maximum attainable pain relief when they take a
15 pill?

16 That type of look at acute pain studies

1 gives you sort of a feel of how effective that is.

2 If we do that calculation for each of the
3 doses and look at the incremental difference, that
4 would be that increased benefit.

5 Slide on, please.

6 So here, in this table, we sort of
7 combined what you saw on each of those individual
8 bar graphs. And what we had done is listed here.
9 And the Hopkinson is the combination of those
10 three studies, the publication -- that's the first
11 study presented here -- where you see the
12 cumulative percent of subjects, a little bit
13 slightly different of how those studies were
14 run -- of subjects with greater than 50 percent
15 pain relief, the 1,000-milligram dose, and the
16 650, and that delta, or that increased response.

17 We also broke out, because we wanted to
18 see in general, if you're going to look at dose
19 response, you need to look at more severe pain in
20 order to see the differences of the benefit of
21 higher doses. So it's broken out for the very
22 severe pain group, in that cohort.

1 Of the two dental pain studies, a couple
2 of points about those. The dental pain studies in
3 the 1980s were being developed -- 214 were a
4 mixture of dental pain studies. We don't do that
5 nowadays. So we still were able to see that the
6 incremental response is in a range of 17 to 23
7 when you look at the 650 and 1,000.

8 What we did also have is a more recent in
9 the -- 2003 where we had the 500-milligram dose
10 compared to 1,000 -- and that's the last one. And
11 we see that in that particular case, when you look
12 at that meaningful difference, it's about 20
13 percent.

14 So it was our way of taking a look at
15 each individual study and what that incremental
16 benefit would be along the lines of our proposal
17 to take one for those lowest effective dose for
18 people who will get that -- but then that
19 additional benefit for those that would need to
20 take two.

21 DR. HERTZ: Can I just ask a follow-up
22 question? This is Sharon Hertz back here from

1 FDA.

2 So when you look at this -- the
3 Hopkinson, et al, combined in a post-hoc
4 meta-analysis, correct? And then the very severe
5 pain in the second row is that same post-hoc
6 analysis further for just the very severe pain --
7 is that correct?

8 DR. GELOTTE: Yes, that's the very severe
9 pain group.

10 DR. HERTZ: And when you looked at any of
11 these studies individually, were you able to
12 detect any differences? And when you looked at
13 the pain that might be more comparable to the OTC
14 use -- so when you didn't just look at the severe
15 pain, but when you looked at the more moderate
16 pain, did you notice any difference between the
17 doses at that point?

18 DR. GELOTTE: Well, as Dr. Chang
19 mentioned as well, when she presented the data,
20 what you use today for acute pain is the third
21 molar impaction studies for OTC drugs, whether
22 it's ibuprofen or not, to be able to separate

1 between doses.

2 So, again, these studies were old and
3 they had, I guess, a mixture of moderate and
4 severe pain. So that's why we broke that out.

5 However, we do have the most definitive
6 study in terms of the differences between doses,
7 this 02156, which represents that modern study.

8 DR. HERTZ: Right, but that wasn't
9 actually my question. My question -- I'm pretty
10 familiar with pain outcomes, because I kind of do
11 that every day.

12 And my question is, with your analyses of
13 these studies that you've done in preparation for
14 this, or whenever this was prepared, did you --
15 you looked at the severe pain to try and get more
16 separation of the doses, but what was the analysis
17 of the not most severe pain, which might be more
18 comparable for OTC?

19 DR. GELOTTE: There wouldn't be
20 separation.

21 DR. HERTZ: Okay.

22 DR. NELSON: Okay. There's only one

1 person left on the first time question asker list,
2 and that's me, and I'm going to not ask my
3 question, because it's now 5:30, and I'll hold my
4 question till tomorrow. So everybody else should
5 feel that they've gotten their chance to ask
6 questions, and we'll have more time tomorrow --
7 believe me -- to discuss this.

8 Okay. So in the spirit of the Federal
9 Advisory Committee Act and the Government in the
10 Sunshine Act, we act that advisory committee
11 members take care that any conversation about
12 today's topic take place in the open forum of this
13 meeting and not in private conversations this
14 evening.

15 We would like to thank the press in
16 advance for their consideration in refraining from
17 asking questions of the committee until the press
18 conference that will occur at the end of the day
19 tomorrow, on Tuesday.

20 Committee members, please take your white
21 binders with you, and remember to bring it with
22 you tomorrow at 8:00 a.m. when we meet back in

1 this room. Thank you.

2 (Whereupon, the proceedings adjourned at
3 5:28 p.m.)