www.archive.org
415.561.6767
415.840-0391 e-fax

Internet Archive
300 Funston Avenue
San Francisco, CA 94118

AFFIDAVIT OF CHRISTOPHER BUTLER

1. I am the Office Manager at the Internet Archive, located in San Francisco, California. I make this declaration of my own personal knowledge.

2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.

3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to surf more than 150 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a list of available dates. The visitor may select one of those dates, and then begin surfing on an archived version of the Web. The links on the archived files, when served by the Wayback Machine, point to other archived files (whether HTML pages or images). If a visitor clicks on a link on an archived page, the Wayback Machine will serve the archived file with the closest available date to the page upon which the link appeared and was clicked.

4. The archived data made viewable and browseable by the Wayback Machine is compiled using software programs known as crawlers, which surf the Web and automatically store copies of web files, preserving these files as they exist at the point of time of capture.

5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]. Thus, the Internet Archive URL http://web.archive.org/web/19970126045828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date assigned by the Internet Archive applies to the HTML file but not to image files linked therein. Thus images that appear on a page may not have been archived on the same date as the HTML file. Likewise, if a website is designed with "frames," the date assigned by the Internet Archive applies to the frameset as a whole, and not the individual pages within each frame.

6. Attached hereto as Exhibit A are true and accurate copies of printouts of the Internet Archive's records of the HTML files for the URLs and the dates specified in the footer of the printout.

7. I declare under penalty of perjury that the foregoing is true and correct.

DATE: 6/15/12

Christopher Butler

CALIFORNIA JURAT WITH AFFIANT STATEMENT

See Attached Document.

State of California
County of San Francisco

Subscribed and ~~sworn to (~~or affirmed) before me this 15th day of June, 2012, by Christopher Butler,

proved to me on the basis of satisfactory evidence to be the person who appeared before me.

NANCY CHEUNG
COMM. #1876791
Notary Public-California
SAN FRANCISCO COUNTY
My Comm. Exp. FEB 9, 2014

Signature: _____

Exhibit A

FDA ADVISORY COMMITTEES

[NOTE: Many of the documents are in PDF format, the ADOBE ACROBAT Reader is needed to review PDF files. Click on the ADOBE icon below and download the free reader.]

- Federal Advisory Committee Act
- Executive Secretaries (Updated 8/1/00)
- CDER Rosters
- List of Advisory Committees & Information Line Numbers
- Meeting Transcripts/Minutes/Other Docs by Center
  - 1997 [Transcripts] / [Minutes]
  - 1998 (Transcripts / Minutes)
  - 1999 (Meeting documents by Center)
  - 2000 (Meeting documents by Center)
  - 2001 (Meeting documents by Center)
- Selected Transcripts
  - Accutane
  - Rezulin
  - Redux (Three Frequently Requested Transcripts)
  - 1996 (including Mifepristone)
- What's New

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[Home] [Up] [CBER 2001 Meeting Documents] [CDER 2001 Meeting Documents]
[CDRH 2001 Meeting Documents][OC 2001 Meeting Documents]
[Federal Registers] [FDA Home Page][What's New]

2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 07/30/01)
- Blood Products Advisory Committee (Updated 08/14/01)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 10/12/01)
- Vaccines & Related Biologic Products Advisory Committee (Updated 08/17/01)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 10/15/01)
- Anti-Viral Drugs Advisory Committee (Updated 10/17/01)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 10/10/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
- Nonprescription Drugs Advisory Committee (Updated 10/18/01)
- Oncologic Drugs Advisory Committee (Updated 09/27/01)
- Peripheral and Central Nervous System Drugs Advisory Committee (Updated 07/13/01)
- Advisory Committee for Pharmaceutical Science (Updated 10/03/01)
- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
- Pulmonary-Allergy Drugs Advisory Committee (Updated 10/18/01)

Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
- Circulatory System Devices Panel (Updated 09/27/01)
- Gastroenterology-Urology Devices Panel (Updated 09/07/01)
- General and Plastic Surgery Devices Panel (Updated 08/07/01)
- Medical Devices Dispute Resolution Panel (Updated 09/21/01)
- Microbiology Devices Panel (New 10/11/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 08/14/01)
- Orthopedic and Rehabilitation Devices Panel (Updated 08/22/01)
- Radiologic Devices Panel (Updated 6/13/01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

Office of the Commissioner (OC)

- Ranch Hand Advisory Committee (New 08/02/01)
- Science Board to FDA (Updated 10/11/01)

[Accessibility] [E-mail]

Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

(Updated 10/18/01)

2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 11/23/01)
- Blood Products Advisory Committee (Updated 12/10/01)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 11/26/01)
- Vaccines & Related Biologic Products Advisory Committee (Updated 11/27/01)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 12/10/01)
- Anti-Viral Drugs Advisory Committee (Updated 12/11/01)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 10/24/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
- Nonprescription Drugs Advisory Committee (Updated 10/18/01)
- Oncologic Drugs Advisory Committee (Updated 12/05/01)
- Peripheral and Central Nervous System Drugs Advisory Committee (Updated 07/13/01)
- Advisory Committee for Pharmaceutical Science (Updated 12/12/01)
- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
- Pulmonary-Allergy Drugs Advisory Committee (Updated 10/18/01)

Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
- Circulatory System Devices Panel (Updated 11/26/01)
- Clinical Chemistry and Clinical Toxicology Devices Panel (Updated 11/23/01)
- Gastroenterology-Urology Devices Panel (Updated 10/26/01)
- General and Plastic Surgery Devices Panel (Updated 08/07/01)
- Medical Devices Dispute Resolution Panel (Updated 11/26/01)
- Microbiology Devices Panel (New 11/05/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 11/29/01)
- Orthopedic and Rehabilitation Devices Panel (Updated 08/22/01)
- Radiologic Devices Panel (Updated 01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

Office of the Commissioner (OC)

- Ranch Hand Advisory Committee (New 08/02/01)
- Science Board to FDA (Updated 12/05/01)

Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

(Updated 12/12/01)

2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 11/23/01)
- Blood Products Advisory Committee (Updated 01/08/02)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 03/29/02)
- Vaccines & Related Biologic Products Advisory Committee (Updated 01/03/02)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 05/23/02)
- Anti-Viral Drugs Advisory Committee (Updated 01/23/02)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 12/21/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
- Nonprescription Drugs Advisory Committee (Updated 10/18/01)
- Oncologic Drugs Advisory Committee (Updated 01/18/02)
- Peripheral and Central Nervous System Drugs Advisory Committee (Updated 07/13/01)
- Advisory Committee for Pharmaceutical Science (Updated 12/21/01)
- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
- Pulmonary-Allergy Drugs Advisory Committee (Updated 10/18/01)

Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
- Circulatory System Devices Panel (Updated 12/20/01)
- Clinical Chemistry and Clinical Toxicology Devices Panel (Updated 12/20/01)
- Gastroenterology-Urology Devices Panel (Updated 10/26/01)
- General and Plastic Surgery Devices Panel (Updated 12/20/01)
- Medical Devices Dispute Resolution Panel (Updated 11/26/01)
- Microbiology Devices Panel (New 11/05/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 12/20/01)
- Orthopedic and Rehabilitation Devices Panel (Updated 08/22/01)
- Radiologic Devices Panel (Updated 01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

National Center for Toxicological Research (NCTR)

- Ranch Hand Advisory Committee (New 08/02/01)

Office of the Commissioner (OC)

- Science Board to FDA (Updated 02/07/02)

Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

Updated 05/23/02

CDER 2001 Meeting Documents

Anti-Infective Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
4/26	4/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02quest.pdf, htm Slides 3746s1.htm
4/23	4/23	3744t1_01.pdf & htm	3744t1.rtf		Notice of Mtg. 032301d.htm & pdf Briefing Information 3744b1.htm Agenda 3744a1.pdf, htm Roster 3744r1.pdf, htm Questions 3744q1.pdf, htm Slides 3744s1.pdf
	4/24	3744t2.pdf & htm	3744t2.rtf		Briefing Information 3744b2.htm Agenda 3744a2.pdf, htm Roster 3744r2.pdf, htm Questions 3744q2.pdf, htm Slides 3744s2.pdf
01/30	01/30	3719t1_01.pdf (6126) 3719t1_02.pdf (6374) 3719t1_03.pdf (6385) 3719t1_04.pdf (6428)	3719t1.rtf (439)	3719m1.doc, pdf	Briefing Package 3719b1.htm Roster 3719r1.htm Slides 3719s1.htm Agenda 3719a1.htm

					Question 3719q1.htm

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Anti-Viral Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
2/27	2/27	3731t1_01.pdf (6394) 3731t1_02.pdf (6275) 3731t1_03.pdf (3920)	3731t1.rtf (271)		Agenda 3731a1.doc, pdf Slides 3731s1.htm Roster 3731r1.doc, pdf 3731r2.doc, pdf Briefing Information 3731b1.htm Questions 3731q1.doc, pdf
1/10	1/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm Slides 3676s1.htm 3676s1_03.pdf
	1/11	3678t1_a.pdf 3678t1_b.pdf 3678t1_c.pdf 3678t1_d.pdf	3578t1.rtf		Agenda 3678a1.doc, pdf Briefing Information 3678b1.htm Slides 3678s1.htm

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Arthritis Advisory Committee					
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4/19	4/20	3740t1_01.pdf 3740t1_02.pdf 3740t1_03.pdf	3740t1.rtf		Agenda 3740a1.htm & pdf Briefing Information 3740b1.htm Questions 3740q1.htm & pdf Roster 3740r1_01 htm & pdf 3740r1_02 htm & pdf Slides 3740s1.htm

2/7	2/7	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		Agenda 3677a1.doc, pdf Roster 3677r1_01.doc, pdf Guest Roster 3677r1_02.doc, pdf Briefing Information 3677b1.htm Questions 3677q1.doc, pdf Slides 3677s1.htm
	02/08	3677t2_01.pdf (6774) 3677t2_02.pdf (6852) 3677t2_03.pdf (2918)	3677t2.rtf (597)		Briefing Package 3677b2.htm Agenda 3677a2.doc & pdf Questions 3677q2_01.doc & pdf 3677q2_02.doc & pdf Slides 3677s2.htm

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Cardiovascular and Renal Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
5/24	5/24				Briefing Information 3749b1.htm Agenda 3749a1.pdf & htm Questions 3749q1.pdf & htm
	5/25				Briefing Information 3749b2.htm Questions 3749q2.pdf & htm

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Nonprescription Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
05/11	05/11				Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Briefing Information 3737b1.htm Petition

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Oncologic Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
06/07	06/07				Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
4/24	4/24	3743t1_01.pdf 3743t1_02.pdf 3743t1_03.pdf	3743t1.rtf		Agenda 3743a1.htm & pdf Briefing Information 3743b1.htm & pdf

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Peripheral & Central Nervous System Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
6/6	6/6				Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm
3/13	3/13	3724t1.pdf	3724t1.rtf	3724m1.htm 3742m1.pdf	Agenda 3724a1.doc, pdf Roster 3724r1_01.doc, pdf Briefing Info 3724b1.htm Slides 3724s1.htm
	3/14	3724t2.pdf	3724t2.rtf	3724m2.htm 3724m2.pdf	Agenda (DRAFT) 3724a2.doc, pdf Roster 3724r1_02.doc, pdf Briefing Info 3724b2.htm Slides 3724s2.htm

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Pharmaceutical Science Drugs Advisory Committee

Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID
Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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2/14	2/14	3685t1.pdf, txt		3685m1.pdf	Agenda 3685a1.doc, pdf Roster 3685r1.doc, pdf Questions 3685q1.doc, pdf Briefing Info 3685b1.htm Slides 3685s.htm
	2/15	3685t2.pdf, txt		3685m2.pdf	Agenda 3685a2.doc, pdf Roster 3685r2.doc, pdf Questions 3685q2.doc, pdf Briefing Info 3685b2.htm

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Pulmonary-Allergy Drugs Advisory Committee					
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05/11	05/11				Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Briefing Information 3737b1.htm Petition

[Federal Registers] [FDA Home Page][Dockets Home Page][CBER][CDRH][OC][Up][AC What's New] [Accessibility] [E-mail] Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee					
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09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			
4/26	4/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm
4/23	4/23	3744t1_01.pdf & htm	3744t1.rtf		Notice of Mtg. 032301d.htm & pdf Briefing Information 3744b1.htm Agenda 3744a1.pdf, htm Roster 3744r1.pdf, htm Questions 3744q1.pdf, htm Slides 3744s1.pdf
	4/24	3744t2.pdf & htm	3744t2.rtf		Briefing Information 3744b2.htm

					Agenda 3744a2.pdf, htm Roster 3744r2.pdf, htm Questions 3744q2.pdf, htm Slides 3744s2.pdf
01/30	01/30	3719t1_01.pdf (6126) 3719t1_02.pdf (6374) 3719t1_03.pdf (6385) 3719t1_04.pdf (6428)	3719t1.rtf (439)	3719m1.doc, pdf	Briefing Package 3719b1.htm Roster 3719r1.htm Slides 3719s1.htm Agenda 3719a1.htm Question 3719q1.htm

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Anti-Viral Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
10/03	10/03				Draft Agenda 3792a1.pdf & htm Final Agenda 3792a1.pdf & htm Roster Committee 3792r1_01.pdf & htm Consultants & Guests 3792r1_02.pdf Questions 3792q1.pdf Briefing Information 3792b1.htm
	10/04				Agenda 3792a2.pdf & htm Roster Committee 3792r2_01.pdf & htm Consultants & Guests 3792r2_02.pdf Questions 3792q2.pdf Briefing Information 3792b2.htm
2/27	2/27	3731t1_01.pdf (6394) 3731t1_02.pdf (6275) 3731t1_03.pdf (3920)	3731t1.rtf (271)		Agenda 3731a1.doc, pdf Slides 3731s1.htm Roster 3731r1.doc, pdf 3731r2.doc, pdf

					Briefing Information 3731b1.htm Questions 3731q1.doc, pdf
1/10	1/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm Slides 3676s1.htm
	1/11	3678t1_a.pdf 3678t1_b.pdf 3678t1_c.pdf 3678t1_d.pdf	3578t1.rtf		Agenda 3678a1.doc, pdf Briefing Information 3678b1.htm Slides 3678s1.htm

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Arthritis Advisory Committee					
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8/16	8/16	3779t1.pdf (320)			Agenda 3779a1.htm & pdf Rosters Committee 3779r1_committee.htm & pdf Consultants 3779r1_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf Briefing Information 3779b1.htm Questions 3779q1.htm & pdf Revised Questions 3779q1_revised.htm & pdf Slides 3779s1.htm
	8/17	Pages 1-100 3779t2_01.pdf Pages 101-159 3779t2_02.pdf		3779m2.pdf & htm	Agenda 3779a2.htm & pdf Rosters Committee 3779r2_committee.htm & pdf Consultants 3779r2_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf

					Briefing Information 3779b2.htm
4/19	4/20	3740t1_01.pdf 3740t1_02.pdf 3740t1_03.pdf	3740t1.rtf		Agenda 3740a1.htm & pdf Briefing Information 3740b1.htm Questions 3740q1.htm & pdf Roster 3740r1_01 htm & pdf 3740r1_02 htm & pdf Slides 3740s1.htm
2/7	2/7	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		Agenda 3677a1.doc, pdf Roster 3677r1_01.doc, pdf Guest Roster 3677r1_02.doc, pdf Briefing Information 3677b1.htm Questions 3677q1.doc, pdf Slides 3677s1.htm
	02/08	3677t2_01.pdf (6774) 3677t2_02.pdf (6852) 3677t2_03.pdf (2918)	3677t2.rtf (597)		Briefing Package 3677b2.htm Agenda 3677a2.doc & pdf Questions 3677q2_01.doc & pdf 3677q2_02.doc & pdf Slides 3677s2.htm

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Cardiovascular and Renal Drugs Advisory Committee					
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08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal

					3775q1_02.pdf, htm Slides 3775s1.htm
	08/10	Pages 1-100 3775t2_01.pdf Pages 101-200 3775t2_02.pdf Pages 201-228 3775t2_03.pdf	3775t2.rtf (299)		Briefing Information 3775b2.htm Questions bosenton 3775q2.pdf, htm
5/24	5/24	3749t1_01.pdf (9171) 3749t1_02.pdf (8690) 3749t1_03.pdf (7469) 3749t1_04.pdf (4025)	3749t1.rtf (437)		Briefing Information 3749b1.htm Agenda 3749a1.pdf & htm Questions 3749q1.pdf & htm
	5/25	3749t2_01.pdf (9171) 3749t2_02.pdf (8465) 3749t2_03.pdf (8352) 3749t2_04.pdf (7345)	3749t2.rtf (465)		Briefing Information 3749b2.htm Questions 3749q2.pdf & htm

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Endocrinologic and Metabolic Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
07/26	07/26	Pages 1-100 3761t1_01.pdf (9,446) Pages 101-200 3761t1_02.pdf (9,613) Pages 201-300 3761t1_03.pdf (9,586) Pages 301-342 3761t1_04.pdf (8,306)	3761t1.htm	3761m1.pdf & htm	Notice of Meeting June 8, 2001 txt pdf Agenda 3761a1.pdf, htm Questions 3761q1.pdf, htm Briefing Information 3761b1.htm Slides 3761s1.htm
	07/27	Pages 1-100 3761t2_01.pdf (8,398) Pages 101-200 3761t2_02.pdf (8,508) Pages 201-300 3761t2_03.pdf (8,318) Pages 301-359 3761t2_04.pdf (9,991)	3761t2.htm	3761m2.pdf & htm	Agenda 3761a2.pdf, htm Questions 3761q2.pdf, htm Roster 3761r2.pdf, htm Briefing Information 3761b2.htm Slides 3761t2.htm

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Nonprescription Drugs Advisory Committee					
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05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Briefing Information 3737b1.htm Petition

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Oncologic Drugs Advisory Committee					
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09/10	09/10	Morning Session Pages 1-100 3782t1_01a.pdf (10,008) Pages 101-179 3782t1_01b.pdf Afternoon Session Pages 1-100 3782t1_02a.pdf (9,796) Pages 101-200 3782t1_02b.pdf (9,878) Pages 201-225 3782t1_02c.pdf (2,226)	Morning Session 3782t1_01.htm (139) Afternoon Session 3782t1_02.htm		Agenda 3782a1.pdf & htm Revised Agenda 3782a1_revised.pdf & htm Roster 3782r1.pdf & htm Consultants 3782r1_consultants.pdf & htm Questions 3782q1.pdf & htm Intradose 3782q1_02. pdf & htm Briefing Information 3782b1.htm Slides 3782s1.htm
	09/11	Pages 1-100 3782t2_01.pdf Pages 101-200 3782t2_02.pdf Pages 201-239 3782t2_03.pdf	3782t2.htm		Briefing Information 3782b2.htm Questions 3782q2_zevalin.pdf & htm Slides 3782s2.htm
Pediatric Subcommittee					
06/28	06/28	Pages 1-100 3756t1_01.pdf Pages 101-200 3756t1_02.pdf Pages 201-end 3756t1_03.pdf	3756t1.rtf, 3756t1.txt		Agenda 3756a1.htm, pdf Roster 3756r1.htm, pdf Briefing Information htm & pdf Slides 3756s1.htm
06/07	06/07	Pages 1-100 3757t1_01.pdf Pages 101-201 3757t1_02.pdf	3757t1.txt, htm		Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
Pediatric Subcommittee					

4/24	4/24	3743t1_01.pdf 3743t1_02.pdf 3743t1_03.pdf	3743t1.rtf		Agenda 3743a1.htm & pdf Roster 3743r1.htm, pdf Briefing Information 3743b1.htm & pdf Slides 3743s1.htm

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Peripheral & Central Nervous System Drugs Advisory Committee					
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6/6	6/6	Pages 1-100 3754t1_01.pdf Pages 101-200 3754t1_02.pdf Pages 201-300 3754t1_03.pdf Pages 301-381 3754t1_04.pdf	3754t1.txt	3754m1.pdf, html	Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
3/13	3/13	3724t1.pdf	3724t1.rtf	3724m1.htm 3742m1.pdf	Agenda 3724a1.doc, pdf Roster 3724r1_01.doc, pdf Briefing Info 3724b1.htm Slides 3724s1.htm
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Advisory Committee for Pharmaceutical Science					
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07/19	07/19	Pages 1-100	3763t1.htm, txt	3763m1.htm &	Agenda

		3763t1_01.pdf Pages 101-200 3763t1_02.pdf Pages 201-300 3763t1_03.pdf Pages 301-313 3763t1_04.pdf		pdf	3763a1.htm & pdf Roster 3763r1.htm & pdf Guest Roster 3763r1_guest.doc & pdf FDA Roster 3763r1_fda.doc & pdf Questions 3763q2.htm & pdf Briefing Information 3763b1.htm Slides 3763s1.htm
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Orally Inhaled and Nasal Drug Products Subcommittee					
7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt		Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides 3764s1.htm
Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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Pulmonary-Allergy Drugs Advisory Committee					
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(Updated 10/02/01)

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee

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11/07	11/07				Final Agenda [Word version] [pdf version] [htm version] Draft Agenda [Word version] [pdf version] [htm version] Questions [Word version] [pdf version] [htm version] Briefing Information htm
10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm
09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			

04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm
04/23	04/23	3744t1_01.pdf & htm	3744t1.rtf		Notice of Mtg. 032301d.htm & pdf Briefing Information 3744b1.htm Agenda 3744a1.pdf, htm Roster 3744r1.pdf, htm Questions 3744q1.pdf, htm Slides 3744s1.pdf
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Anti-Viral Drugs Advisory Committee					
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10/03	10/03	Pages 1 - 100 3792t1_01.pdf (9,207)	3792t1.htm		Draft Agenda 3792a1.pdf & htm

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	10/04	Pages 1 - 100 3792t2_01.pdf (9,357) Pages 101-200 3792t2_02.pdf (9,375) Pages 201-300 3792t2_03.pdf (9,990) Pages 301-327 3792t2_04.pdf (8,452)	3792t2.htm		Agenda 3792a2.pdf & htm Roster Committee 3792r2_01.pdf & htm Consultants & Guests 3792r2_02.pdf Questions 3792q2.pdf Briefing Information 3792b2.htm Slides 3792s2.htm
02/27	02/27	3731t1_01.pdf (6394) 3731t1_02.pdf (6275) 3731t1_03.pdf (3920)	3731t1.rtf (271)		Agenda 3731a1.doc, pdf Slides 3731s1.htm Roster 3731r1.doc, pdf 3731r2.doc, pdf Briefing Information 3731b1.htm Questions 3731q1.doc, pdf
01/10	01/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm Slides 3676s1.htm
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Arthritis Advisory Committee

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08/16	08/16	3779t1.pdf (320)			Agenda 3779a1.htm & pdf Rosters Committee 3779r1_committee.htm & pdf Consultants 3779r1_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf Briefing Information 3779b1.htm Questions 3779q1.htm & pdf Revised Questions 3779q1_revised.htm & pdf Slides 3779s1.htm
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Cardiovascular and Renal Drugs Advisory Committee					
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10/11	10/11				Agenda 3793a1.htm & pdf Briefing Information Questions 3793q1.htm & pdf Slides 3793s1.htm
08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal 3775q1_02.pdf, htm Slides 3775s1.htm
	08/10	Pages 1-100 3775t2_01.pdf Pages 101-200 3775t2_02.pdf Pages 201-228 3775t2_03.pdf	3775t2.rtf (299)		Briefing Information 3775b2.htm Questions bosenton 3775q2.pdf, htm
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	5/25	3749t2_01.pdf (9171) 3749t2_02.pdf (8465) 3749t2_03.pdf (8352) 3749t2_04.pdf (7345)	3749t2.rtf (465)		Briefing Information 3749b2.htm Questions 3749q2.pdf & htm

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Endocrinologic and Metabolic Drugs Advisory Committee					
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07/26	07/26	Pages 1-100 3761t1_01.pdf (9,446) Pages 101-200 3761t1_02.pdf (9,613) Pages 201-300 3761t1_03.pdf (9,586) Pages 301-342 3761t1_04.pdf (8,306)	3761t1.htm	3761m1.pdf & htm	Notice of Meeting June 8, 2001 txt pdf Agenda 3761a1.pdf, htm Questions 3761q1.pdf, htm Briefing Information 3761b1.htm Slides 3761s1.htm
	07/27	Pages 1-100 3761t2_01.pdf (8,398) Pages 101-200 3761t2_02.pdf (8,508) Pages 201-300 3761t2_03.pdf (8,318) Pages 301-359 3761t2_04.pdf (9,991)	3761t2.htm	3761m2.pdf & htm	Agenda 3761a2.pdf, htm Questions 3761q2.pdf, htm Roster 3761r2.pdf, htm Briefing Information 3761b2.htm Slides 3761t2.htm

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Nonprescription Drugs Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					
05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Roster Consultants 3737r1_01.htm & pdf Members 3737r1_02.htm & pdf Open Public Hearing 3737r1_03.htm & pdf Briefing Information 3737b1.htm

					Petition Slides 3737s1.htm Open Public Hearing Presentations 3737op1.htm

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Oncologic Drugs Advisory Committee					
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Pediatric Subcommittee					
11/28	11/28				Draft Agenda 3803a1.[Word version] [htm version] [pdf version] Roster 3803r1.[Word version] [htm version] [pdf version] Questions 3803q1. [Word version] [htm version] [pdf version] Briefing Information 3803b1.htm
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Pediatric Subcommittee					
06/28	06/28	Pages 1-100 3756t1_01.pdf Pages 101-200 3756t1_02.pdf Pages 201-end 3756t1_03.pdf	3756t1.rtf, 3756t1.txt		Agenda 3756a1.htm, pdf Roster 3756r1.htm, pdf Briefing Information htm & pdf Slides 3756s1.htm

06/07	06/07	Pages 1-100 3757t1_01.pdf Pages 101-201 3757t1_02.pdf	3757t1.txt, htm		Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
Pediatric Subcommittee					
4/24	4/24	3743t1_01.pdf 3743t1_02.pdf 3743t1_03.pdf	3743t1.rtf		Agenda 3743a1.htm & pdf Roster 3743r1.htm, pdf Briefing Information 3743b1.htm & pdf Slides 3743s1.htm

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Peripheral & Central Nervous System Drugs Advisory Committee					
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6/6	6/6	Pages 1-100 3754t1_01.pdf Pages 101-200 3754t1_02.pdf Pages 201-300 3754t1_03.pdf Pages 301-381 3754t1_04.pdf	3754t1.txt	3754m1.pdf, html	Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
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Advisory Committee for Pharmaceutical Science					
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Nonclinical Studies Subcommittee					
11/13	11/13				Draft Agenda 3798a1. [htm format] & [pdf format] Roster Committee Members [htm format] & [pdf format] Guests [htm format] & [pdf format] Briefing Information 3798b1.htm
07/19	07/19	Pages 1-100 3763t1_01.pdf Pages 101-200 3763t1_02.pdf Pages 201-300 3763t1_03.pdf Pages 301-313 3763t1_04.pdf	3763t1.htm, txt	3763m1.htm & pdf	Agenda 3763a1.htm & pdf Roster 3763r1.htm & pdf Guest Roster 3763r1_guest.doc & pdf FDA Roster 3763r1_fda.doc & pdf Questions 3763q2.htm & pdf Briefing Information 3763b1.htm Slides 3763s1.htm
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Orally Inhaled and Nasal Drug Products Subcommittee					
7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt	3764m1.htm & pdf	Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides 3764s1.htm

Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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Pulmonary-Allergy Drugs Advisory Committee					
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Joint meeting with Nonprescription Drugs Advisory Committee					

05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Roster Consultants 3737r1_01.htm & pdf Members 3737r1_02.htm & pdf Open Public Hearing 3737r1_03.htm & pdf Briefing Information 3737b1.htm Petition Slides 3737s1.htm Open Public Hearing Presentations 3737op1.htm

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(Updated 11/07/01)

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
11/07	11/07	Pages 1-100 (8,448) Pages 101-200 (8,549) Pages 201-307 (17,286)	[Word version] [htm version]	[pdf version] [htm version] [Word version]	Final Agenda [Word version] [pdf version] [htm version] Draft Agenda [Word version] [pdf version] [htm version] Questions [Word version] [pdf version] [htm version] Briefing Information htm Slides
10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm

09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm
04/23	04/23	3744t1_01.pdf & htm	3744t1.rtf		Notice of Mtg. 032301d.htm & pdf Briefing Information 3744b1.htm Agenda 3744a1.pdf, htm Roster 3744r1.pdf, htm Questions 3744q1.pdf, htm Slides 3744s1.pdf
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01/30	01/30	3719t1_01.pdf (6126) 3719t1_02.pdf (6374) 3719t1_03.pdf (6385) 3719t1_04.pdf (6428)	3719t1.rtf (439)	3719m1.doc, pdf	Briefing Package 3719b1.htm Roster 3719r1.htm Slides 3719s1.htm Agenda 3719a1.htm Question 3719q1.htm

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Anti-Viral Drugs Advisory Committee					
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12/12	12/12				Notice of Meeting [text version] [pdf version] Draft Agenda 3819a1_draft [pdf version] [htm version] [Word version] Roster 3819r1_committee [pdf version] [htm version] [Word version] Briefing Information 3819b1.htm
10/03	10/03	Pages 1 - 100 3792t1_01.pdf (9,207) Pages 101-200 3792t1_02.pdf (9,581) Pages 201-300 3792t1_03.pdf (10,067) Pages 301-326 3792t1_04.pdf (8,207)	3792t1.htm		Draft Agenda 3792a1.[pdf version] [htm version] Final Agenda 3792a1.[pdf version] [htm version] Roster Committee 3792r1_01.[pdf version] [htm version] Consultants & Guests 3792r1_02.[pdf version] [htm version] Questions 3792q1.pdf Briefing Information 3792b1.htm Slides 3792s1.htm
	10/04	Pages 1 - 100 3792t2_01.pdf (9,357) Pages 101-200 3792t2_02.pdf (9,375) Pages 201-300 3792t2_03.pdf (9,990) Pages 301-327 3792t2_04.pdf (8,452)	3792t2.htm		Agenda 3792a2.pdf & htm Roster Committee 3792r2_01.pdf & htm Consultants & Guests 3792r2_02.pdf Questions 3792q2.pdf Briefing Information 3792b2.htm Slides 3792s2.htm
02/27	02/27	3731t1_01.pdf (6394) 3731t1_02.pdf (6275) 3731t1_03.pdf (3920)	3731t1.rtf (271)		Agenda 3731a1.doc, pdf Slides 3731s1.htm Roster 3731r1.doc, pdf 3731r2.doc, pdf Briefing Information 3731b1.htm Questions 3731q1.doc, pdf
01/10	01/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm

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Arthritis Advisory Committee					
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08/16	08/16	3779t1.pdf (320)			Agenda 3779a1.htm & pdf Rosters Committee 3779r1_committee.htm & pdf Consultants 3779r1_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf Briefing Information 3779b1.htm Questions 3779q1.htm & pdf Revised Questions 3779q1_revised.htm & pdf Slides 3779s1.htm
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04/19	04/19	3740t1_01.pdf 3740t1_02.pdf 3740t1_03.pdf	3740t1.rtf		Agenda 3740a1.htm & pdf Briefing Information 3740b1.htm Questions 3740q1.htm & pdf Roster 3740r1_01 htm & pdf

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02/07	02/07	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		Agenda 3677a1.doc, pdf Roster 3677r1_01.doc, pdf Guest Roster 3677r1_02.doc, pdf Briefing Information 3677b1.htm Questions 3677q1.doc, pdf Slides 3677s1.htm
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Cardiovascular and Renal Drugs Advisory Committee					
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10/11	10/11				Agenda 3793a1.htm & pdf Briefing Information Questions 3793q1.htm & pdf Slides 3793s1.htm
08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal 3775q1_02.pdf, htm Slides 3775s1.htm

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5/24	5/24	3749t1_01.pdf (9171) 3749t1_02.pdf (8690) 3749t1_03.pdf (7469) 3749t1_04.pdf (4025)	3749t1.rtf (437)		Briefing Information 3749b1.htm Agenda 3749a1.pdf & htm Questions 3749q1.pdf & htm
	5/25	3749t2_01.pdf (9171) 3749t2_02.pdf (8465) 3749t2_03.pdf (8352) 3749t2_04.pdf (7345)	3749t2.rtf (465)		Briefing Information 3749b2.htm Questions 3749q2.pdf & htm

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Endocrinologic and Metabolic Drugs Advisory Committee					
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07/26	07/26	Pages 1-100 3761t1_01.pdf (9,446) Pages 101-200 3761t1_02.pdf (9,613) Pages 201-300 3761t1_03.pdf (9,586) Pages 301-342 3761t1_04.pdf (8,306)	3761t1.htm	3761m1.pdf & htm	Notice of Meeting June 8, 2001 txt pdf Agenda 3761a1.pdf, htm Questions 3761q1.pdf, htm Briefing Information 3761b1.htm Slides 3761s1.htm
	07/27	Pages 1-100 3761t2_01.pdf (8,398) Pages 101-200 3761t2_02.pdf (8,508) Pages 201-300 3761t2_03.pdf (8,318) Pages 301-359 3761t2_04.pdf (9,991)	3761t2.htm	3761m2.pdf & htm	Agenda 3761a2.pdf, htm Questions 3761q2.pdf, htm Roster 3761r2.pdf, htm Briefing Information 3761b2.htm Slides 3761t2.htm

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Nonprescription Drugs Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					
05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf

		Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf			Questions 3737q1.htm, pdf Roster Consultants 3737r1_01.htm & pdf Members 3737r1_02.htm & pdf Open Public Hearing 3737r1_03.htm & pdf Briefing Information 3737b1.htm Petition Slides 3737s1.htm Open Public Hearing Presentations 3737op1.htm

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Oncologic Drugs Advisory Committee					
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12/05	12/05				Draft Agenda 3815a1 [pdf version] [htm version] [Word version] Briefing Information Morning Session 3815b1_01.htm Afternoon Session 3815b1_02.htm
	12/06				Briefing Information Morning Session 3815b2_01.htm Afternoon Session 3815b2_02.htm
Pediatric Subcommittee					
11/28	11/28				Draft Agenda 3803a1.[Word version] [htm version] [pdf version] Roster 3803r1.[Word version] [htm version] [pdf version] Questions 3803q1. [Word version] [htm version] [pdf version] Briefing Information 3803b1.htm Slides 3803s1.htm
09/10	09/10	Morning Session Pages 1-100 3782t1_01a.pdf (10,008) Pages 101-179 3782t1_01b.pdf Afternoon Session Pages	Morning Session 3782t1_01.htm (139) Afternoon Session 3782t1_02.htm		Agenda 3782a1.pdf & htm Revised Agenda 3782a1_revised.pdf & htm Roster

		1-100 3782t1_02a.pdf (9,796) Pages 101-200 3782t1_02b.pdf (9,878) Pages 201-225 3782t1_02c.pdf (2,226)			3782r1.pdf & htm Consultants 3782r1_consultants.pdf & htm Questions 3782q1.pdf & htm Intradose 3782q1_02. pdf & htm Briefing Information 3782b1.htm Slides 3782s1.htm
	09/11	Pages 1-100 3782t2_01.pdf Pages 101-200 3782t2_02.pdf Pages 201-239 3782t2_03.pdf	3782t2.htm		Briefing Information 3782b2.htm Questions 3782q2_zevalin.pdf & htm Slides 3782s2.htm
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06/28	06/28	Pages 1-100 3756t1_01.pdf Pages 101-200 3756t1_02.pdf Pages 201-end 3756t1_03.pdf	3756t1.rtf, 3756t1.txt		Agenda 3756a1.htm, pdf Roster 3756r1.htm, pdf Briefing Information htm & pdf Slides 3756s1.htm
06/07	06/07	Pages 1-100 3757t1_01.pdf Pages 101-201 3757t1_02.pdf	3757t1.txt, htm		Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
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4/24	4/24	3743t1_01.pdf 3743t1_02.pdf 3743t1_03.pdf	3743t1.rtf		Agenda 3743a1.htm & pdf Roster 3743r1.htm, pdf Briefing Information 3743b1.htm & pdf Slides 3743s1.htm

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Peripheral & Central Nervous System Drugs Advisory Committee

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6/6	6/6	Pages 1-100 3754t1_01.pdf Pages 101-200 3754t1_02.pdf Pages 201-300	3754t1.txt	3754m1.pdf, html	Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html

		3754t1_03.pdf Pages 301-381 3754t1_04.pdf			Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
3/13	3/13	3724t1.pdf	3724t1.rtf	3724m1.htm 3742m1.pdf	Agenda 3724a1.doc, pdf Roster 3724r1_01.doc, pdf Briefing Info 3724b1.htm Slides 3724s1.htm
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Advisory Committee for Pharmaceutical Science					
Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
11/28	11/28				Revised Agenda [pdf version] [htm version] [Word version] Draft Agenda 3804a1 [pdf version] Rosters Committee: 3804r1 [pdf version] [htm version] [Word version] Guests: [pdf version] [htm version] [Word version] Briefing Information 3804b1.htm Slides
	11/29				Revised Agenda [pdf version] [htm version] [Word version] Committee: 3804r1 [pdf version] [htm version]

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			Nonclinical Studies Subcommittee		
11/13	11/13	Pages 1-100 (10,038) Pages 101-148 (6,901)	[htm version] [Word version]	[pdf] [htm] [Word]	Draft Agenda 3798a1. [htm format] & [pdf format] Roster Committee Members [htm format] & [pdf format] Guests [htm format] & [pdf format] Briefing Information 3798b1.htm
07/19	07/19	Pages 1-100 3763t1_01.pdf Pages 101-200 3763t1_02.pdf Pages 201-300 3763t1_03.pdf Pages 301-313 3763t1_04.pdf	3763t1.htm, txt	3763m1.htm & pdf	Agenda 3763a1.htm & pdf Roster 3763r1.htm & pdf Guest Roster 3763r1_guest.doc & pdf FDA Roster 3763r1_fda.doc & pdf Questions 3763q2.htm & pdf Briefing Information 3763b1.htm Slides 3763s1.htm
	7/20	Pages 1-100 3763t2_01.pdf Pages 101-171 3763t2_02.pdf	3763t2.htm, txt	3763m2.htm & pdf	Agenda 3763a2.htm & pdf Guest Roster 3763r2_guest.doc & pdf FDA Roster 3763r2_fda.doc & pdf Slides 3763s2.htm
			Orally Inhaled and Nasal Drug Products Subcommittee		
7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt	3764m1.htm & pdf	Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides

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Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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2/14	2/14	3685t1.pdf	3685t1.txt	3685m1.pdf	Agenda 3685a1.doc, pdf Roster 3685r1.doc, pdf Questions 3685q1.doc, pdf Briefing Info 3685b1.htm Slides 3685s1.htm
	2/15	3685t2.pdf	3685t2.txt	3685m2.pdf	Agenda 3685a2.doc, pdf Roster 3685r2.doc, pdf Questions 3685q2.doc, pdf Briefing Info 3685b2.htm Slides 3685s2.htm

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Pulmonary-Allergy Drugs Advisory Committee					
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Joint meeting with Nonprescription Drugs Advisory Committee					
05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Roster

		3737t1_04.pdf			**Consultants 3737r1_01.htm & pdf** **Members 3737r1_02.htm & pdf** **Open Public Hearing 3737r1_03.htm & pdf** **Briefing Information** 3737b1.htm Petition **Slides** 3737s1.htm **Open Public Hearing Presentations** 3737op1.htm

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(Updated 12/12/01)

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. This meeting has been rescheduled for January 30-31, 2002. You may find additional information at CDER 2002 page.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee

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11/07	11/07	Pages 1-100 (8,448) Pages 101-200 (8,549) Pages 201-307 (17,286)	[Word version] [htm version]	[pdf version] [htm version] [Word version]	Final Agenda [Word version] [pdf version] [htm version] Draft Agenda [Word version] [pdf version] [htm version] Questions [Word version] [pdf version] [htm version] Briefing Information htm Slides
10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm

09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)	pdf htm doc	Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm Questions pdf htm doc
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Anti-Viral Drugs Advisory Committee

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12/12	12/12	Pages 1-100 Pages 101-200 Pages 201-211	doc htm		Notice of Meeting [text] [pdf] Draft Agenda [pdf] [btm] [Word] Final Agenda [pdf] [btm] [Word] Questions [pdf] [btm] [Word] Roster Committee [pdf] [btm] [Word] Consultants & Guests [pdf] [btm] [Word] Briefing Information Slides
10/03	10/03	Pages 1 - 100 pdf (9,207) Pages 101-200 pdf (9,581) Pages 201-300 pdf (10,067) Pages 301-326 04.pdf (8,207)	btm		Draft Agenda [pdf] [btm] Final Agenda [pdf] [btm] Roster Committee [pdf] [btm] Consultants & Guests [pdf] [btm] Questions pdf Briefing Information Slides
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Arthritis Advisory Committee					
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08/16	08/16	3779t1.pdf (320)			Agenda 3779a1.htm & pdf Rosters Committee 3779r1_committee.htm & pdf Consultants 3779r1_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf Briefing Information 3779b1.htm Questions 3779q1.htm & pdf Revised Questions 3779q1_revised.htm & pdf Slides 3779s1.htm
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04/19	04/19	3740t1_01.pdf 3740t1_02.pdf 3740t1_03.pdf	3740t1.rtf		Agenda 3740a1.htm & pdf Briefing Information 3740b1.htm Questions 3740q1.htm & pdf

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Cardiovascular and Renal Drugs Advisory Committee					
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10/11	10/11	Morning Session Pages 1-100 pdf Pages 101-129 pdf Afternoon Session Pages 130-229 pdf Pages 230-274 pdf	[Word] [htm]		Agenda 3793a1.htm & pdf Briefing Information Questions 3793q1.htm & pdf Slides 3793s1.htm
08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal 3775q1_02.pdf, htm

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Nonprescription Drugs Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					

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Pediatric Subcommittee					
11/28	11/28	Morning Session Pages 1-100 pdf Pages 101-202 pdf Afternoon Session Pages 203-302 pdf Pages 303-405 pdf	[Word] [htm]		Draft Agenda 3803a1.[Word version] [htm version] [pdf version] Roster 3803r1.[Word version] [htm version] [pdf version] Questions 3803q1. [Word version] [htm version] [pdf version] Briefing Information

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Peripheral & Central Nervous System Drugs Advisory Committee

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Advisory Committee for Pharmaceutical Science					
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Orally Inhaled and Nasal Drug Products Subcommittee					
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Non-Clinical Studies Subcommittee					
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Psychopharmacologic Drugs Advisory Committee					
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Pulmonary-Allergy Drugs Advisory Committee					
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Joint meeting with Nonprescription Drugs Advisory Committee					

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CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. This meeting has been rescheduled for January 30-31, 2002. You may find additional information at CDER 2002 page.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm

09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)	pdf htm doc	Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm Questions pdf htm doc
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08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal 3775q1_02.pdf, htm

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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					

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Peripheral & Central Nervous System Drugs Advisory Committee

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Advisory Committee for Pharmaceutical Science					
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Updated 05/23/02

PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Briefing Information

Consideratin of NDA 21-196, Xyrem (sodium oxybate, Orphan Medial Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons wit narcolepsy.

Orphan Medical Presentations

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

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Xyrem Prescription and Distribution Process, *Video Script 2/2/01)* html pdf

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PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Briefing Information

Consideratin of NDA 21-196, Xyrem (sodium oxybate, Orphan Medial Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons wit narcolepsy.

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PEDIATRIC SUBCOMMITTEE OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Slides

Consideration of (NDA) 21-196, Xyrem® (sodium oxybate, Orphan Medical, Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

Orphan Medical Presentations ppt html

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

NDA 21196 Xyrem for Narcolepsy, Orphan Medica, Inc., Comments About Sleepwalking, Ranjit Mani, MD pdf htm

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Zvosec, Deborah L. PhD, Stephen W. Smith, MD. et al, "Adverse Evens, Including Death, Associate with the Use of 1,4-butanediol," *N Engl J Med*, Vol. 344, No. 2, January 11, 2001, pp 87-94.*

Statement of Trinka Porrata pdf

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Statement of Brian A Hunter, Young Adults with Narcolepsy - YAWN pdf

Statement Regarding GHB (Xyrem) Approval, Joe Spillane, PharmD, ABAT pdf htm

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Pediatric Subcommittee of the

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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Pediatric Subcommittee of the

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

April 23, 2001

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Calendar of CDER Advisory Committee Meetings

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This area includes meetings and events that are related to CDER's mission. It is advised that participants verify the time and location of meetings and events. There are other meetings and events listed on the FDA Meetings Page.

Tentative Advisory Committee Meetings (updated 5/8/2001)

- Advisory Committee Agendas
- Advisory Committee Information
- Advisory Committee Transcripts

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
ADVISORS AND CONSULTANTS STAFF

May 2001 Meetings

Cardiovascular and Renal Drugs Advisory Committee

May 24, 2001, from at 8:30 a.m. to 5 p.m. and on May 25, 2001, from at 9 a.m. to 3:30 p.m., National Institutes of Health, 9000 Rockville Pike, Building 10, Clinical Center, Jack Masur Auditorium, Bethesda, MD. **ADDITIONAL INFORMATION**: Joan C. Standaert, Center for Drug Evaluation and Research (HFD-110), 419-259-6211 or John M. Treacy (HFD-21), 301-827-7001. Oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:00 a.m. on May 24, 2001.
Agenda: On May 24, 2001, the committee will discuss: (1) published interim analyses of ALLHAT (antihypertensive and lipid lowering treatment to prevent heart attack trial) sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health; and (2) Response to the Citizen's Petition of Lawrence D. Bernhardt and Arnold Liebman, regarding new drug application (NDA) 19-668, Cardura (doxazosin), Pfizer Inc. On May 25, 2001, the committee will discuss NDA 20-920 Natrecor (nesiritide), Scios Inc., for treatment of acute heart failure.

June 2001 Meetings

Peripheral and Central Nervous System Drugs Advisory Committee

June 6, 2001, 8 a.m. to 5 p.m., Holiday Inn, 8120 Wisconsin Avenue, Bethesda Maryland. The hotel phone number is 301-652-2000.
ADDITIONAL INFORMATION: Sandy Titus, Center for Drug Evaluation and Research (HFD-21), 301/827-7001 or e-mail: Tituss@cder.fda.gov.
Oral presentations from the public will be scheduled between approximately 1

p.m. to 2 p.m.
Agenda: On June 6, 2001, the committee will consider the safety and efficacy of new drug application (NDA) 21-196, Xyrem®, (sodium oxybate, Orphan Medical, Inc.) proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

Background material from the sponsor and the FDA will be posted 24 hours before the meeting in the "Peripheral and Central Nervous System Drugs Advisory Committee" section of the Dockets site. This is the same web site where you can find the minutes, transcript, and slides from the meeting. This material is generally posted about three weeks after the meeting.

The **June 14-15, 2001** meeting of the Anesthetic and Life Support Drugs Advisory committee meeting has been cancelled. The meeting will be rescheduled for Fall 2001.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Wednesday, June 6, 2001

8:15 a.m.

Holiday Inn
Bethesda, Maryland

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PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chairman
Sandra Titus, Ph.D., Executive Secretary

MEMBERS:

Ella P. Lacey, Ph.D., Consumer Representative,

LaRoy P. Penix, M.D.
Richard D. Penn, M.D.
Gerald Van Belle, Ph.D.

CONSULTANTS:

Gustavo C. Roman, M.D.
Jerry S. Wolinsky M.D.

XYREM CONSULTANTS:

VOTING:

Pippa Simpson, Ph.D.
Carol Falkowski, Ph.D.

NON-VOTING:

Christine A. Sannerud, Ph.D.
Jerry Frankenheim, Ph.D.
Jo-Ellen Dyer, Ph.D.

ON PONE-LINK - NON-VOTING:

Ronald Chervin, M.D.
Christian Guilleminault, M.D.

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.
John Feeney, M.D.
Deborah B. Leiderman, M.D.

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C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. KAWAS: Good morning, everyone, and welcome to the Wednesday, June 6, 2001 meeting of the Peripheral and Central Nervous System Advisory Committee. My name is Claudia Kawas, and I think we can begin with introductions, please, perhaps over by Dr. Temple's side.

DR. TEMPLE: Bob Temple, I am the Office Director.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products, FDA.

DR. FEENEY: John Feeney, neurology team leader, FDA.

DR. MANI: Ranjit Mani, medical reviewer, Neuropharm., FDA.

DR. LEIDERMAN: Deborah Leiderman, Director, Controlled Substance Staff, FDA.

DR. SIMPSON: Pippa Simpson, University of Arkansas Medical Sciences, biostatistician.

DR. FALKOWSKI: Carol Falkowski, drug

abuse researcher, Hazelden Foundation.

DR. ROMAN: Gustavo Roman, Professor of Neurology at the University of Texas, San Antonio.

DR. WOLINSKY: Jerry Wolinsky, Professor

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of Neurology, University of Texas, Houston.

DR. TITUS: Sandy Titus, FDA, the administrator of the Peripheral and Central Nervous System Committee.

DR. PENN: Richard Penn, neurosurgeon at the University of Chicago.

DR. LACEY: Ella Lacey, professor emerita, Illinois University, Carbondale, Illinois.

DR. VAN BELLE: Gerald Van Belle, Department of Biostatistics, from the University of Washington.

DR. PENIX: LaRoy Penix, Associate Professor of Neurology at Moorehouse School of Medicine.

DR. SANNERUD: Christina Sannerud, Drug and Chemical Evaluation Section, Drug Enforcement Administration.

DR. DYER: I am Jo Dyer, with the University of California, San Francisco and the San Francisco Poison Control System, California.

DR. FRANKENHEIM: Jerry Frankenheim, pharmacologist, National Institute on Drug Abuse.

DR. KAWAS: Today we have met to discuss the consideration of Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptom

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of daytime sleepiness for persons with narcolepsy. The main focus of the deliberations will also be on risk management issues.

If we could ask Dr. Titus to begin with

the conflict of interest statement?

Conflict of Interest Statement

DR. TITUS: Before I begin the conflict of interest statement, I just want to announce that we have two people on line with us, Dr. Chervin and Dr. Guilleminault. They are both in a room listening to us and will participate with us on the mikes.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The special government employees participating in today's meeting have been screened for interests in Orphan Medical's Xyrem and for interests in the products and sponsors deemed by the agency to be competing. Based on the agency's review of each participant's response to the conflict of interest screening, it has been determined that there is no potential for a

conflict of interest with regard to this meeting.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ronald Chervin would like to disclose for the record that he has a contract with Cephalon to study Provigil, but not for use in narcolepsy. He is the principal investigator, however, no funds from Cephalon, present or past, have contributed to his personal salary and none have been made available for his non-research related use. Further, in previous years Dr. Chervin was a

co-investigator with Cephalon in a narcolepsy clinical trial.

Christian Guilleminault has been the administrator of the Sleep Disorder Clinic in Palo Alto, California, where the study of Xyrem was performed by a team of researchers.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. KAWAS: Thank you very much, Dr. Titus. We will begin with Dr. Russell Katz, of the FDA, who will give us the FDA overview of the issues. I want to point out to the committee members that they have much of the materials that they will be seeing during this meeting in front of them.

FDA Overview

DR. KATZ: Thanks, Claudia. First, I would like to welcome the committee back. You were here just a few months ago so I appreciate your coming back so soon.

We have a number of invited guests who are augmenting the committee today, and many of them are experts in the evaluation of issues related to drug abuse, and I would just like to welcome them,

in particular Drs. Simpson, Sannerud and Frankenheim.

We have two other experts who will actually be speakers later this morning. Dr. Dyer

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will speak on her experience with GHB use and misuse in cases she has seen, and Dr. Falkowski will talk about the epidemiology of GHB abuse in the United States.

Finally, as Dr. Titus mentioned, we have two acknowledged experts in sleep disorders who are attending the annual sleep meetings in Chicago, but who have agreed to sit in a hotel room for however long this takes and participate by phone. So, Drs. Guilleminault and Chervin, wherever you are, thank you. Thanks for being here.

As you know and as you have heard, today we will ask you to discuss NDA 21-196, which was submitted by Orphan Medical for the use of Xyrem, gamma hydroxybutyrate or better known as GHB, for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

GHB is a simple molecule and it is ubiquitous in mammalian tissues, its function though is not really well known. Its relevant regulatory history goes back to about 1990, and prior to that date it was freely available in health food stores. But in 1990 the agency began to receive reports of widespread recreational use in a number of different types of folks, for a

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number of different types of reasons, or GHB and began to get numerous reports of serious adverse events associated with its misuse.

It was not entirely clear that all of

these events were necessarily related to GHB. It was difficult to interpret some of these reports because there were concomitant medications that were unreported and it wasn't entirely clear whether or how much GHB was in a particular preparation that someone had taken. Those sorts of issues made it difficult to completely interpret the reports, but many of the reports were of events that were known to be consistent with GHB's effect as a potent CNS depressant, including things like respiratory depression, coma and other decreased levels of consciousness. So, it was reasonable to believe that GHB was at least in part responsible for some of these reports.

As a result of these reports, the agency withdrew GHB from health food shelves and made it illegal to use. However, illicit use continued and continues to this day, not only with GHB but with two related drugs which are precursors, GBL and 1,4-butanediol, and there have been similar reports of serious adverse events associated with the use

of those products.

So, against this background of use, the investigation of GHB as a treatment for cataplexy began. Based on the results of a single trial performed by the sponsor and their commitment to perform additional trials, the sponsor was granted a treatment IND in December of 1998. For those of you unfamiliar with a treatment IND, it is basically a mechanism to permit use of an investigational drug outside the context of a controlled trial for a serious disease for which there aren't other available treatments. It is usually granted relatively late in the development

of a drug so that by the time you grant it you have some reasonable idea, based on controlled data, that the drug is probably effective and reasonably well tolerated.

Just another relevant piece of history, in 2000 Congress passed a law which placed GHB in Schedule I and also placed it into Schedule III for any approved uses that may be granted.

The NDA that we are discussing today was submitted in September of 2000 by the company, and it contains the results of four controlled trials which the sponsor believes establish substantial

evidence of effectiveness for cataplexy and excessive daytime sleepiness in patients with narcolepsy. It also contains, obviously, safety experience.

I just want to talk about the safety experience for just a little bit. As you know from the briefing documents, much of the safety data in the application was not generated by the company but by an individual investigator under his own individual investigator IND. This is Dr. Scharf, and he is an acknowledged expert in the use of GHB and he has been treating patients under his IND for about 16 years. His data comprise almost 30 percent of the patient safety database in the NDA. If one looks at patient time, his experience constitutes about 70 percent of the total patient exposure.

As part of a routine investigation of the NDA to look at source documents, the agency investigators found that they were unable to locate some critical source documents of Dr. Scharf's IND,

and it was difficult to confirm the sponsor's submission of Dr. Scharf's data. However, subsequent to that, Dr. Scharf has made extensive efforts to provide the additional source documents

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and agency investigators have reinspected that data. I believe the conclusion of that investigation is that we find that the records, for the most part, do support the sponsor's descriptions of Dr. Scharf's data. And, we believe we can make certain statements about that data at this point.

We were particularly interested in the 80 or so patients that Dr. Scharf treated that did not move on into the company's treatment IND. He treated a total of 143, or thereabouts, patients, 60 of whom went into the sponsor's treatment IND. So, we had a good idea of what was happening to those patients but there were about 80 that didn't and who were basically discontinued from treatment under Dr. Scharf's own IND.

So, except for a handful of patients, we believe we know why those 80 patients discontinued and their status. I believe we can say reasonably comfortably say that nothing catastrophic that we don't know about happened to those patients but, unfortunately, we have relatively little well-documented data regarding other less serious adverse events in that cohort of 80. Other than patient diaries, we have essentially no

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documentation about exactly what dose those patients took and for how long.

I have gone into this at some depth because the safety experience in the NDA is

relatively small as compared to a typical NDA, and that is by agreement. This is an orphan product. Based on the sponsor's estimated prevalence of cataplexy of about 25,000, it received orphan designation and one wouldn't necessarily expect that a safety database of a typical size, which is somewhere in at least 10000 to 2000 patients in the typical NDA, would be submitted in an orphan application. So, we agreed with the sponsor that about 500 patients treated for appropriate durations, at appropriate doses would be acceptable.

But, given the relatively small database and some of these residual questions about a reasonable proportion of it, that is to say Dr. Scharf's data, that may take on some additional meaning and we would like you to think about that as the day goes on.

In addition to the safety and the effectiveness data which is required in an NDA of course, the sponsor has proposed a detailed risk

management program, and that has three goals: to inform patients and physicians about the risks of GHB; to minimize the risks to those patients; and also to minimize the likelihood that subjects for whom the drug has not been prescribed will be exposed to it. This latter point not only refers to diversion and its use illicitly by folks who shouldn't be taking it, but also to the accidental use of GHB in the home, perhaps by small children, and you will hear how GHB is administered and what form it is prepared in, and we think that is a potential risk. So, we would like you to think about that as the day goes on too.

As far as the risk management program, you will hear about it in great detail from the company but, in brief, it consists of a couple of sort of major components. One is that the product will be made available through a central pharmacy and will be shipped directly to the patient at home. Physicians and patients will also receive detailed materials about the risks and the appropriate use of the drug after the first prescription is filled. Actually, they will receive those materials initially and all subsequent refills of prescriptions will be contingent upon patients and

physicians documenting that they have read these materials, and they understand the risks and how to take the drug appropriately.

All patients and physicians will be entered into a registry, and there will be close surveillance instituted to ensure that untoward events are minimized, for example, to ensure that patients don't go from doctor to doctor trying to get refills of prescriptions that are inappropriate.

So, with these data and against the background of misuse of GHB out in the population at large, we bring you today's application and we will ask you to formally vote on three questions. One is whether or not you think that substantial evidence of effectiveness has been submitted for the indications that the sponsor has proposed, that is to say, cataplexy and excessive daytime sleepiness in patients with narcolepsy. If you find that they haven't, we would be very interested to know whether or not you feel that substantial

evidence has been submitted for either of those two indications.

While you listen to the effectiveness data, we would like you to pay particular attention

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to the question of dose and for which dose you think evidence of effectiveness has been submitted. If you find there is substantial evidence of effectiveness for a particular indication, we need to ask you whether or not GHB can be considered safe in use given appropriate labeling. Now, we are not going to discuss necessarily the specifics of proposed labeling but, nonetheless, we ask you to think of it in that context.

Again, in assessing the safety of the product, we ask you to concentrate on at least the question of what dose you have found to be effective and whether or not there is sufficient safety experience at that dose for the drug to be approved.

Finally, we want to take a formal vote on the question of whether or not you think it is required or should be required that the drug be approved only with the risk management program of some type, not necessarily the one specifically proposed by the company. Obviously, the company has proposed a risk management program but we need to know whether or not you think it is mandatory that it be approved with such a program in place. If you do, we have a number of questions that we

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would like you to discuss -- not necessarily take a formal vote on but discuss with regard to a risk management program and some of the provisions that the sponsor has proposed.

There are some aspects of the program that they have proposed that we would like you to pay particular attention to and discuss. For example, there is some considerable sympathy in the agency for including a provision in the risk management program that would restrict the use of the drug to patients with whatever indication you believe has been supported, that is to say, to restrict as much as possible off-label prescribing. That is one possibility.

There is also some enthusiasm internally for physicians and patients to document that they have reviewed the relevant materials before the first prescription is filled. So, we would like you to think about that as well as we talk about the risk management program.

So, as you can see from the agenda, the company is going to present the safety and effectiveness data, after which Dr. Mani, from the Division, will come up and present briefly some of our views about the data you will have just heard.

Specifically, I believe we have some different views about the evidence submitted for establishing a claim for excessive daytime sleepiness in narcolepsy, and there may be other additional safety issues that we would like to bring up at that time, in particular the question of an event that has been called sleep walking.

I think with that as background, I will turn it back to Dr. Kawas. Thank you.

DR. KAWAS: Thank you, Dr. Katz. Orphan Medical presentation is to follow. Dr. David Reardan, Orphan Medical?

Orphan Medical Presentation

DR. REARDAN: Hi. Good morning. Good morning, ladies and gentlemen, members of the committee and FDA.

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My name is David Reardan, and I represent Orphan Medical as head of regulatory affairs. Orphan Medical is a small, 60-person firm, dedicated to the development of orphan drugs. We have obtained marketing approval for six orphan products from FDA since we were founded, in 1994.

The firm became involved with Xyrem when approached by FDA that same year, and Xyrem was

designated an orphan drug in 1994. Today we will share with you the data that has been collected with respect to the efficacy and safety since our IND was submitted, in 1996.

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Dr. Mignot, director of the Narcolepsy Institute at Stanford University, will present a picture of a narcoleptic patient and the serious medical need such patients have for new therapeutic treatments.

Dr. Houghton is the chief medical officer and chief operating officer at Orphan Medical, and he will present next on the efficacy that has been collected. Dr. Houghton was chair of anesthesia and critical care in Australia.

Dr. Black, director of the Stanford Sleep Clinic and an investigator for several trials, will share with you the EEG pharmacology of Xyrem. Dr. Houghton will then present the safety data and finish up with a benefit/risk assessment.

Following presentations by two FDA invited

speakers with respect to GHB abuse, Dr. Balster, director of the Institute for Drug and Alcohol Studies at the Medical College of Virginia, will share with you his views on abuse liability.

Since there is public abuse of GHB and its analogs, the company has developed a risk management program for Xyrem that will be presented by Patti Engel, our vice president of marketing and sales.

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In addition to those presenting today, the following experts are available in the audience to answer questions from the committee or FDA: Dr. Emsellem, Dr. Hagaman and Dr. Ristanovic are all directors of their respective sleep institutes, and have been investigators in our clinical trials. Dr. Okerholm is a consultant in the area of pharmacokinetics and drug metabolism; Dr. Reno in the area of toxicology; and Dr. Richard Trout, who is a professor emeritus in statistics from Rutgers, is here if there are any statistical questions.

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This is the chemical structure of sodium oxybate, more commonly known as gamma hydroxybutyrate, or GHB. Notice that it is a simple 4-carbon hydroxy fatty acid and, as such, quite easy to synthesize. In fact, kits have been illegally promoted on the Internet for its manufacture. If an amino group were to replace

this alcohol functional group at position 4, you would have GABA, gamma aminobutyric acid, another CNS active chemical. Oxybate is a natural compound in the human body.

[Slide]

Gamma hydroxybutyrate was first discovered in the 1960's by Dr. Labore, in France, and was investigated as an analog for GABA. It was found to have hypnotic properties and was first approved in France, and later a few other countries of Europe, as an adjunct in anesthesia. It was used in labor and delivery for quite a few years. The injectable form is still available today in parts of Europe.

In the 1970's initial work was begun in Canada to test its properties in narcolepsy. Following initial promise for use in patients with narcolepsy two controlled trials were conducted by independent investigators, one in the U.S. and one in The Netherlands. In 1994, due to the promising investigator trials, FDA Office of Orphan Products approached Orphan Medical to consider the compound for development.

Since there was no patent protection and the market was very small, no other firms were

willing to consider the development of GHB for narcolepsy at the time. Orphan Medical agreed to sponsor this medication. Our new drug application was submitted in October of 2000 and was designated by FDA for priority review.

The clinical development has been fairly straightforward and all controlled trials conducted to date have shown sodium oxybate to be effective and safe for the treatment of narcolepsy. This project has been made more difficult because of the abuse situation.

[Slide]

Let me explain why Xyrem is not going to

be a factor in the abuse of GHB and its precursors. Orphan Medical was aware abuse existed at the time the company agreed to sponsor development of Xyrem. At this same time, Internet was burgeoning. Due to its ease of synthesis and ready availability of precursor chemicals, GHB was initially an easy target for promoters of illegal drugs.

But GHB is not the only problem. GBL and 1,4-butanediol are precursor chemicals that can be easily converted to GHB and are, in fact, converted to GHB in the human body. These precursors are widely available as bulk chemicals and are being

illegally used in the United States, and the abuse problem is growing.

Federal legislation, enacted in 2000, helped to control the availability of GHB and GBL but not 1,4-butanediol and other precursor chemicals that can be used for the same purpose. In many states, even with GHB schedules, GBL and 1,4-butanediol are not controlled.

We believe that approval of Xyrem for use by patients with narcolepsy will not add to the general abuse problem of GHB and its numerous precursors.

[Slide]

The proposed indication for which we are asking FDA for marketing approval is to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

[Slide]

Narcolepsy fits the definition of orphan disease in the United States, with less than 200,000 patients. There are estimated to be about

135,000 patients, of which 55 percent are diagnosed, with about 24,000 seeking treatment for cataplexy.

[Slide]

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I would now like to introduce you to Dr. Emmanuel Mignot, from Stanford. Dr. Mignot has been widely published in this area and is considered one of the premiere international experts on narcolepsy. He has not participated in any of our clinical trials.

Medical Need

DR. MIGNOT: It is my privilege to talk to you today about narcolepsy. I have been working on narcolepsy for about 15 years, both at the level of basic research as well as clinical care. I am a medical doctor and I see patients with narcolepsy.

[Slide]

I am going to try to summarize in a few minutes really a lot of data about narcolepsy and how it impacts people.

[Slide]

First, I would like to start briefly by reviewing the symptoms of narcolepsy. Narcolepsy is usually associated with 5 different symptoms. The most disabling and the most problematic in patients with narcolepsy is sleepiness. Patients with narcolepsy are sleepy all the time; tired; they have sleep attacks; they cannot stay awake for a long period of time, and it is usually why they

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come to see the doctor. They just cannot live a normal life. Especially in work conditions, as you probably know, it is very difficult -- you have to be awake all day long and it is a major problem in

narcolepsy.

Now, it is not enough to diagnose narcolepsy. Narcolepsy is not just sleepiness and there are a lot of other medical conditions that are associated with sleepiness. Patients with narcolepsy also have a series of symptoms that correspond to the fact that they go very quickly into rapid eye movement sleep. As probably many of you know, rapid eye movement sleep is a stage of sleep that only occurs 1.5 or 2 hours after you fall asleep where you are actively dreaming but your body is completely paralyzed and you have these rapid eye movements.

Patients with narcolepsy go into REM sleep extremely quickly, sometimes in a few minutes, and that leads to a series of symptoms where patients sometimes are half way through REM sleep, being still awake. Consequently, they may experience odd symptoms that we call the dissociated REM sleep event, abnormal REM sleep event. Those are cataplexy, hypnagogic hallucinations and sleep

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paralysis.

An example is cataplexy. When a patient gets emotionally excited, typically when they are happy, they meet a good friend, sometimes when they are angry but most often when they are joking, in a nice environment and happy about something, they may feel suddenly weak; they become paralyzed; sometimes they fall down to the ground, completely paralyzed and they cannot move. In very rare cases they may even go into REM sleep. We believe somehow being emotionally excited stimulates the paralysis of rapid eye movement sleep that every one of us experiences during sleep, except that in

patients with narcolepsy it may occur in the middle of the day in response to emotion.

Also, when they fall asleep they sometimes have hallucinations because they go so quickly into REM that sometimes they dream while they are still awake. I remember a patient, for example, who every night would fall asleep and he would see someone coming and strangling him. Or, they may hear people talking; or see people walking in the room. It can be very frightening and it can be a very terrible experience for patients with narcolepsy.

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Another symptom of abnormal REM sleep that patients with narcolepsy have as well is called sleep paralysis. When they wake up from a nap or when they fall asleep, sometimes they again go so quickly into REM and disassociated REM sleep events that sometimes they may be paralyzed from REM but still be awake. Basically, they would wake up from sleep and they cannot move, not even their little finger. It can be very scary. It lasts a few minutes and then finally they can move. Some patients with narcolepsy have multiple episodes of sleep paralysis when they nap during the day, and so forth, and that is another very bothersome symptom.

Finally, patients with narcolepsy, contrary to what people way, don't sleep too much; their main problem is that they just cannot stay awake. They fall asleep very quickly in many circumstances, but they are unable to stay asleep for a long period of time. In fact, patients with narcolepsy don't sleep 20 hours a day. What

happens is that at night they don't sleep well. Often that is another symptom that is very bothesome. They fall asleep very quickly at night but after one hour they cannot sleep again. They

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are just awake and cannot sleep.

Then, all these symptoms are quite severe and, of course, affect the lives of patients. And, since GHB is recommended in cataplexy, which is muscle atonia triggered by emotion, I will just show you a quick video of a patient with cataplexy.

This is a boy, a 9-year old. Narcolepsy usually starts during adolescence and here the clinicians are trying to make him laugh to just try to elicit the symptom, and you see he is falling down and he is completely paralyzed and he is losing his muscle tone. Some of these patients have that many time per day and it can be extremely socially disabling. You can imagine being at a party or being with some friends and having this happen to you. In this kid it was particularly severe.

Most cases of narcolepsy start during adolescence but occasionally it starts as early as 5 years of age. It peaks around 15 years of age. It is often extremely problematic because I am sure you realize when you have this type of thing happening to you and sleepiness at school, especially when you are 15 years old, when you are an adolescent, it really wrecks your life apart,

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especially when it is not properly diagnosed.

[Slide]

There have been a number of studies, and I won't have time to review them, that have shown

that the quality of life of patients with narcolepsy is extremely impaired, as much as depression, epilepsy or other reference conditions in almost all the scales that you look at. Clearly, it is a very socially disabling disorder.

[Slide]

It is also, of course, a disorder that impacts just your daily life. For example, driving -- patients with narcolepsy have a very increased rate of accidents and sometimes many of them refuse to drive just because of falling asleep or having cataplexy while driving.

[Slide]

We have objective tests for diagnosing narcolepsy. In fact, it is not just a psychological disorder. You can actually use a test like the Multiple Sleep Latency Test, where you ask patients to come to the sleep lab. You check that they sleep normally and the following day you ask them to nap every two hours and you measure how fast they fall asleep. You see,

normally people won't fall asleep or nap in the middle of the day, or they would fall asleep with a 15-minute latency in the dark. A patient with narcolepsy, as soon as you switch off the light, they are sleeping. In a few minute latency, they are asleep. So, we have objective ways to show that these people have a problem.

[Slide]

Also, in this nap you see that they go very quickly into REM sleep. Normal people won't have REM sleep before one hour after falling asleep, but patients with narcolepsy will go straight into REM. You can actually demonstrate --

we call that sleep onset REM period -- that patients with narcolepsy have all this sleep abnormality and REM abnormality using sleep testing.

[Slide]

Current treatment for narcolepsy is completely symptomatic. We don't treat the cause of the disease; we only treat the symptoms. Typically, the treatment now uses two drugs, two lines of drug. A patient with cataplexy will be treated usually with two drugs. One is a stimulant which would be a classical amphetamine-like

stimulant or this more recent drug that was just approved that is called modafinil, Provigil, which works on sleepiness. It will keep a patient awake but will never normalize him; it only improves him. And, they all have a lot of side effects. You know, the stimulants can even produce psychosis in some rare cases but, of course, they raise blood pressure. They produce psychological changes. They have a lot of other side effects.

We all know now that they all increase dopamine in the brain. We have done a series of studies which have shown that. Even modafinil, the most recent drug -- we know now that it works by increasing dopamine in the brain. And, they don't have anything different from each other so some of them are definitely safer than others.

For the antidepressants, for the treatment of cataplexy -- this works well on sleepiness but it doesn't work on cataplexy or nightmares, or hallucination or sleep paralysis. For this you use antidepressants. Why? Because antidepressants

depress REM sleep and they also suppress cataplexy and all the other abnormal dreaming that patients with narcolepsy have. The problem is they also have a lot of side effects. Actually, the new

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SSRI, they don't work as well as the old tricyclines. Often you even have to use the old tricycline antidepressants because norepinephrine uptake inhibition seems to be the mode of action of these drugs, more than serotonin. They don't really work that well and, of course, they have a lot of side effects and a lot of different problems.

[Slide]

Finally, I want to stress again that we need new treatments for narcolepsy just because all the treatments we have now just don't make people normal. They just help them to be better. You can best illustrate that using the MSLT/MWT, which is a slightly different test where, instead of measuring how fast people fall asleep in the dark, you ask people to try to stay away in the dark and you see that normal people can stay awake. They don't fall asleep in 20 minutes, whereas patients with narcolepsy fall asleep very dramatically after a few minutes in the dark.

Even if you treat them with modafinil which is a very good treatment for narcolepsy, which was recently approved, you improve them but they never become normal. Then, it is clear that

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what we have is not enough. We just need better, and this would be the same for amphetamines. Even high dose amphetamines don't normalize these patients. That has been shown by multiple studies.

[Slide]

We have worked for more than 15 years trying to find the cause of narcolepsy, and recently we have isolated the gene for narcolepsy in a canine model where the disease is genetically determined, and we found that it was a receptor for a norpeptide that is called hypocretin. We found that in humans with narcolepsy it is not like dogs with narcolepsy; it is not the receptor but a peptide called hypocretin which is expressed in about 10,000 cells in the brain, here in the hypothalamus, which is missing in patients with narcolepsy.

This is brain tissue of a patient with narcolepsy. You see here is the normal; everything is gone. If you measure in the cerebrospinal fluid, this is a normal level in a normal person, or in patients with MS or other neurological symptoms, and you see in all patients with narcolepsy that this hypocretin molecule is gone. We know now that the cause of narcolepsy is not

dopamine or norepinephrine, which is the current treatment for narcolepsy, which are stimulants and antidepressants acting through these neurotransmitters, and probably replacing this hypocretin would be an ideal treatment for narcolepsy. But this finding was only made one year ago and it is going to take probably 10 years or many years before we actually have a treatment based on this new discovery.

[Slide]

To summarize the medical need, I think I have convinced you that narcolepsy is a serious and disabling condition that needs treatment, and these

patients are in desperate need of better treatment. As you will see from the presentation afterwards, GHB is one of the effective treatments which helps a lot of people. So, current treatments like amphetamines and antidepressants don't work well in terms of efficacy. They have a lot of side effects. They all work the same way but they don't act on the cause of the disease and, clearly, we know that GHB, even though it probably doesn't act on hypocretin, acts differently from other drugs. And, it is one more drug that would be available to help a lot of patients with narcolepsy.

Finally, even though there have been numerous, very recent developments that are very exciting in the hypocretin area, unfortunately, you all know it takes a long time until drugs are available and it is going to take probably many years until this available.

This is a very quick summary of what we know about narcolepsy to date. Thank you.

DR. REARDAN: Thank you, Dr. Mignot. Dr. Houghton will now present the data which has been assembled in support of the efficacy of Xyrem. Dr. Houghton is a qualified anesthesiologist, with 18 years of clinical experience in critical care medicine and numerous years experience in pharmaceutical drug development. Bill?

Efficacy

DR. HOUGHTON: Good morning.

[Slide]

I am sorry to start with such a complex diagram but this just outlines the pattern of studies that we will be talking about this morning.

On the left-hand side here are the 4 controlled studies on which the assessment of efficacy will be based, but what is unusual about this program is that patients, in an uncommon way, move to

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extension protocols. So, as Dr. Katz pointed out, even though the total database may be small, the total duration of exposure of patients is quite promising.

The first study that I will talk about is entitled OMC-GHB-3, and the patients, at the completion of this short-term treatment study did progress to a long-term, open label study and then had the opportunity to move into one of the treatment IND protocols, with some of them still participating in that study.

A second contributor to that protocol was the patients who completed the first 6-month safety treatment IND protocol, and the significance of all of that is that it was from this protocol that the patients are represented in the long-term pivotal blinded efficacy study that supports the long-term efficacy of Xyrem.

[Slide]

The first and pivotal study is a randomized, double-blind, placebo-controlled, parallel group, multi-center trial comparing the effects of three doses, 3 g, 6 g and 9 g of orally administered Xyrem with placebo for the treatment of narcolepsy. As I mentioned, this was a study

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conducted in 136 patients in 16 centers.

[Slide]

The primary efficacy parameter was the change in the number of total cataplexy attacks in

the last two weeks of the treatment period compared to the two weeks of the baseline period.

Secondary efficacy parameters that were considered included complete and partial cataplexy attacks; daytime sleepiness; inadvertent sleep attacks during the day; hypnagogic hallucinations; sleep paralysis; and a clinical global impression of change.

[Slide]

Patients naive to sodium oxybate therapy were chosen with a bona fide diagnosis of narcolepsy for at least 6 months. They were required to have a record of a polysomnograph or Multiple Sleep Latency Test within the last 5 years to exclude other causes of daytime sleepiness, and particularly sleep apnea.

They were required to have a history of daytime sleepiness and cataplexy for at least 6 months, and recurrent daytime naps that occurred almost daily in the preceding 3 months.

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The overall study design was divided into 5 stages. Firstly, there was a screening period in which the patients were required to qualify for entry criteria and then withdrawn from their existing anti-cataplectic medications over a 4-week period to avoid rebound phenomena which were considered a safety consideration. At the end of this withdrawal period they entered a washout period, which was determined by at least 5 times the half-life of their preceding drug to remove any effects of those drugs. However, if patients weren't on any cataplectic medications, they were still required to remain 5 days in that washout

period to familiarize themselves with the use of diaries.

They then proceeded to a baseline period of 2 to 3 weeks, using daily diary recording to establish the severity of their disease and to confirm that they had reached a stable stage in their disease. They then entered a 4-week blinded, randomized treatment period, with a visit at 2 weeks, a telephone call the day after commencing treatment, and then safety telephone calls 3 times a week during the treatment period, at the end of which they were abruptly withdrawn from drug and

followed up 3 to 5 days later to assess any rebound phenomena and any adverse experiences that may have ensued.

[Slide]

As is shown here, the patient groups were very evenly balanced at baseline. They represented a fairly severe group of narcoleptics, with an average incidence of cataplexy of around 34 per week at baseline.

There was a dose-response relationship across the doses based on median change in the total number of cataplexy attacks that, when compared to placebo, approached significance at the 9 g dose, with a p value of 0.0529, and achieved highly significant change at the 9 g dose.

[Slide]

This dose relationship is clearly shown in the plot of median change from baseline in the number of cataplexy attacks per week, and the spread of the data is demonstrated as the quartile lines around these median values.

[Slide]

A more clinically relevant presentation of the data is the percentage change in the number of cataplexy attacks from baseline. This was

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calculated as the distribution of percentage change values for each individual patient and is again presented as the medians. This representation clearly shows that the major change in cataplexy occurs in the first 2 weeks, but with ongoing change in the subsequent 2 weeks, as represented in 2 of the dose groups.

[Slide]

Secondary efficacy variables included assessment of excessive daytime sleepiness using the validated Epworth Sleepiness Scale which rates the patient's feeling of daytime somnolence by scoring on a scale of 0-3 the probability of falling asleep in the circumstances of 8 common life scenarios. This results in a potential maximum score of 24.

[Slide]

This slide demonstrates a clear dose-related reduction in the Epworth Sleepiness Scale, reaching a significant level of 0.0001 in the 9 g group compared to placebo. This change was incremental beyond the effects of stable dosing of stimulants because stimulant medications were maintained constant throughout the study. In all Xyrem-treated groups some patients improved beyond

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the defined narcolepsy range, with some patients in the 6 g and 9 g groups actually improving into the normal range as rated by the Epworth Sleepiness Scale.

The second component of daytime sleepiness, the number of inadvertent naps during the day, was also significantly reduced compared to placebo in the 6 g group and 9 g dosing.

[Slide]

The severity of the disease at baseline was rated by the principal investigator according to the following validated scale. Then, at the end of the treatment period a blinded global impression of change according to the rating shown here was made, rating from very much improved through no change to very much worse.

[Slide]

Assignment of these modal values indicated a primary distribution of the placebo patients mainly to no change or minimally improved, but there is an obvious predominance of assignment in the 9 g dose to very much improved and much improved.

[Slide]

Because of the complexity of presenting

these assigned categories, a post hoc simplification was applied to group the patients that showed clear clinical improvement into a responder group, and all others were called non-responders. This again displays the dose-response trend in the categorical data, with a clear statistical difference between the 9 g group and the placebo group.

[Slide]

Other secondary measures that achieved significant change included the number of awakenings at night, subjective sleep quality, morning alertness, the ability to concentrate.

Hypnagogic hallucinations and sleep paralysis, which had a much lower incidence at baseline, showed a non-significant trend towards improvement.

[Slide]

The next study that I would like to present is the study that was suggested by the FDA to provide evidence of long-term efficacy of Xyrem based on the return of cataplexy following the cessation of long-term treatment with the active drug.

[Slide]

Patients entered this blinded, randomized

study from the long-term open-label study I showed you initially having completed the GHB-2 protocol and proceeded into the GHB-3 protocol for periods up to 2 years, or from the initial treatment IND protocol. This provided assessment of potential adverse consequences of the abrupt withdrawal of long-term therapeutic doses of Xyrem as well.

Patients having taken the drug for 6 months to 3.5 years were screened, and after blinded randomization entered a single blind baseline period in which daily diaries were used to record the severity of their cataplexy. They then entered a double-blind phase of 2 weeks wherein they were randomized in a 50 percent ratio to either continued, unchanged dose of Xyrem in a blinded fashion or to placebo. Randomization was performed in a centralized manner to ensure equal representation of dosing in the comparative groups.

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The primary efficacy variable was the change in the number of cataplexy attacks in the

double-blind period compared to baseline. There was a median change of zero in the Xyrem group but, as seen, there was a marked increase in the incidence of cataplexy in those randomized to

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placebo. This was highly significant.

[Slide]

When the median change from baseline by week was calculated, you can see that there was a step-wise increase in cataplexy which supported the long-term efficacy of the drug in a statistically significant manner, but they represent a gradual return of cataplexy rather than an acute rebound phenomenon.

[Slide]

I will now present very briefly some supportive data from 2 early controlled, crossover design studies that have been published, and for which Orphan Medical purchased the databases and included in the NDA submission.

[Slide]

The first was a study conducted by Dr. Lawrence Scrima, then of the University of Arkansas, in 20 patients, 10 males and 10 females, using a dose of 50 mg/kg, much lower than some of those in the previous studies and equivalent to about 3.5 g per day in a 70 kg man.

Following the withdrawal of anticataplectic medications, he recorded a baseline period during which the patients were required to

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have a minimum of 10 cataplexy attacks, then were randomized into an initial treatment period of 29 days, followed by a washout period of 6 days, and then crossed over to the alternate treatment, again

followed by a washout of 6 days. Stimulants were continued throughout this study and all patients were actually transferred to methylphenidate as their stimulant.

[Slide]

The primary efficacy measures are identified, with the average number of cataplexy attacks compared to baseline and objective sleepiness index as determined by the Multiple Sleep Latency Test. This was to represent a measure of daytime sleepiness.

Because of logistic issues in the study conduct and methodologic issues in design and definition, this is presented as supporting data only to represent cataplexy response at a lower dose. As can be seen, this patient group again represented a reasonably severe narcoleptic population. They had a baseline measure of 20 cataplexy attacks per week. There was an initial fairly significant placebo response, as was shown in the previous studies, but by week 3 and week 4

statistically significant differentiation between placebo and active treatment was shown, and there was a statistically significant overall response in the study. There was no significant change in the sleepiness index as the measure of daytime sleepiness, however, in this study.

[Slide]

The second study that I will present very briefly was conducted by Dr. Lammers, in The Netherlands. It is, again, a randomized, blinded, crossover design study in 24 narcoleptics. The other significant difference in this study was that concomitant medications for both cataplexy and

excessive daytime sleepiness were continued throughout the study.

Following a 1-week baseline to establish disease severity, the patients were randomized to a 4-week treatment period at a dose of 60 mg/kg in divided nightly doses, followed by a washout period of about 3 weeks, and then a baseline period of 1 week again preceding a second treatment period of 4 weeks.

[Slide]

As is obvious here, the severity of cataplexy during the baseline period was much lower

in this study, potentially the consequence of continued anticataplectic medication in some patients. But, again, there is a significant response. According to the statistical plan which was very scant that was represented in the published study, and agreed to by the FDA, there was an incorrect or unsatisfactory statistical management of this study. The change in cataplexy was not statistically significant. When the results of this study were submitted by Orphan, they were reanalyzed with an ANCOVA analysis as had been applied in the GHB-2 study, and this change was significant according to the ANCOVA analysis.

[Slide]

Other measures that showed significant improvement included hypnagogic hallucinations and daytime sleep attacks again.

[Slide]

Although not eligible for determination of efficacy since it is an open-label study, I would like to briefly mention three aspects of the

follow-on study to the pivotal GHB-2 study. And, 117 patients chose to participate entering the study at the 6 g per day dose and then slowly titrating to clinical efficacy between the doses of

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3 g and 9 g. This study, therefore, represents the proposed clinical use of the drug and, although primarily a safety study, represents some important dynamic information.

[Slide]

This slide shows the response in cataplexy over the 12-month period. What is surprising is that the maximum nadir occurred at about 8 weeks, and then the sustained efficacy was maintained across the 12 months in all dose groups.

[Slide]

A similar pattern was seen in the Epworth Sleepiness Scale, which shows the same time frame with maximum response at about 8 weeks, and then maintained efficacy over the course of 12 months in this open-label study. What is also interesting to note is that most of the patients in most dose groups were maintained beyond the defined narcolepsy range.

[Slide]

When the distribution of doses to which the patients were titrated is shown, it is seen that 6 g per day is the most common dose, followed by the 9 g dose group.

[Slide]

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This represents the pattern of dosing seen in other open-label studies where doses were titrated to clinical response. What is important to note is that there is not a change in dosing

between the 6-month and the 12-month dosing groups, suggesting no tolerance development to maintain the dynamic effects shown.

[Slide]

This slide represents the cohort of patients that entered the SXB-21 protocol via the GHB-2 and then GHB-3 protocol. Represented here is the incidence of cataplexy for each individual patient at the baseline in GHB-2. They were then maintained in the study I have just shown you over the course of up to 2 years, and this is the incidence of cataplexy of each of the individual patients in the single-blinded baseline in the SXB-21 protocol. When the paradigm of random assignment to placebo is shown, then there is certainly a demonstration of efficacy between those who were randomized to the placebo group in SXB-21 versus those that maintained their Xyrem treatment, which certainly helps to support the efficacy statement in the GHB-3 protocol.

[Slide]

Finally and to summarize, we have presented data to show efficacy of sodium oxybate to reduce cataplexy in 4-week treatment periods in a dose-related manner that is highly statistically significant at the 9 g dose, and approaching statistical significance at the 6 g dose.

We have presented supportive data demonstrating statistically significant efficacy of the lower doses, and demonstrated statistically significant efficacy in terms of daytime sleepiness, using the Epworth Sleepiness Scale, again at 9 g. In a scale used in the Lammers study at 60 mg/kg daytime sleep attacks were

statistically significantly reduced in all 3 studies. We supported the long-term efficacy of Xyrem with return of cataplexy when blindedly assigned to placebo in the SXB-21 protocol.

[Slide]

I would now like to very briefly summarize the pharmacokinetics studies that were conducted by Orphan Medical.

[Slide]

In total, we conducted 8 clinical pharmacokinetic studies, including 2 studies in narcoleptic patients and 6 in healthy human

volunteers. This slide lists the 8 pharmacokinetic studies by their primary objective.

The studies included a single dose pilot study in 6 narcoleptics, and a second study in narcoleptic patients comparing acute and chronic dosing over an 8-week period. Normal volunteer studies were conducted to examine the kinetics of Xyrem with respect to gender differences, dose proportionality and the effects of food. Also, 3 drug interaction studies were performed with Zolpiden, protriptyline and modafinil as representatives of the 3 classes of drugs used commonly to treat the symptoms of narcolepsy. Lastly, an in vitro study, using human hepatic microzymes, was conducted to assess the effects of oxybate.

[Slide]

I will only present the studies that have a significant message, and in very brief summary form. This slide displays the results of the dose proportionality study that compared nightly dose of

4.5 and 9 g given in 2 equally divided doses at bedtime and 4 hours later. A randomized, 2-day crossover design was utilized, and doubling the dose from 4.5 to 9 g resulted in a nearly 4-fold

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increase in the area under the time concentration curve. The peak plasma concentration and the time to peak concentration changed significantly with doubling the dose, the latter suggesting capacity-limited absorption. C_{max} was higher after the second dose than with the first nightly dose, as has been seen in other studies with divided dosing.

These findings indicate non-linear kinetics and capacity-limited elimination and absorption, as reported in previously published studies.

[Slide]

The results of the effect of food study are displayed graphically on this slide. In this randomized, crossover study 34 healthy subjects were dosed with 4.5 g of Xyrem on 2 occasions 1 week apart, either after an overnight 10.5 hour fast or immediately following a high fat standardized breakfast. After the high fat meal the peak plasma concentration decreased by almost 60 percent. The median time to achieve peak levels increased from 45 minutes to around 2 hours, and the AUC decreased by 37 percent. All of these differences were statistically significant. The

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apparent half-life was not significantly altered. Thus, the presence of food significantly reduces systemic exposure to GHB, a finding not previously reported.

In the 3 volunteer kinetic studies the urinary excretion of Xyrem was measured, and renal excretion was shown to be a minor pathway of elimination, accounting for less than 5 percent of the administered drug.

[Slide]

As an example of the drug interaction studies, on this slide we present the modafinil results. The upper graph indicates that co-administration of 200 mg of modafinil had no impact on the kinetics of Xyrem. The lower graph demonstrates that 4.5 g of Xyrem had no clinically significant effect on the kinetics of a standard dose of modafinil.

Likewise, in the Zolpiden protriptyline interaction studies, no significant kinetic interactions were found. In the separate in vitro study using human hepatic microzymes, sodium oxybate was found to have no effect on 6 cytochrome p450 enzymes either to inhibit or induce their activity.

[Slide]

So in summary, Xyrem oral solution is rapidlyh absorbed and eliminated with a half-life of about one hour. The drug displays non-linear, dose-dependent kinetics, indicative of capacity-limited absorption and elimination. Xyrem kinetics are similar in men and women and do not change with chronic administration at therapeutic doses.

[Slide]

Chronic dosing did not change the kinetics of Xyrem in a patient population, and a high fat

meal appreciably delayed absorption and reduced total systemic exposure to the drug. Three separate in vivo drug interaction studies, as well as the in vitro p450 enzyme study, would suggest the probability of significant drug-drug interaction with Xyrem is minimal. Thank you very much.

DR. REARDAN: Thank you. I would now like to introduce Dr. Jed Black, from Stanford University Sleep Center, and he will present on the polysomnographic effects of Xyrem and GHB.

Polysomnographic Effects of Xyrem

DR. BLACK: Good morning, ladies and

gentlemen. I would like to summarize the body of data that has been collected over the past 25 years which characterizes the effects of gamma hydroxybutyrate or sodium oxybate on sleep parameters. I will then speculate briefly on a possible mechanism whereby these effects on sleep result in a robust improvement in daytime narcolepsy symptoms seen with this agent.

This has been a particular focus of my research in sleep over the past years. That is, how does what happens in the brain at night affect various aspects on daytime function and alertness?

It is unexpected that a medication that objectively markedly improves sleep quality also improves measures of daytime alertness as this finding has never been observed with traditional hypnotics or sleep aids. To pursue an understanding of this possible interaction, 6 investigations have been conducted in humans. These studies explored the effect of sodium oxybate on a variety of nocturnal sleep parameters, using

electroencephalography during sleep and a laboratory test known as polysomnography.

The first 3 studies found an increase in slow wave sleep. Slow wave sleep, also known as

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stages 3 and 4 sleep, is the deepest portion of sleep and correlates positively with functions of daytime concentration, attention and alertness in normal subjects. These studies also reveal a reduction in nocturnal awakenings with GHB.

The more recent studies of Scrima, Lammers and Orphan Medical explored both measures of nocturnal sleep as measured by polysomnography, or PSG, and measures of daytime sleepiness with the Multiple Sleep Latency Test, or daytime alertness with the Maintenance of Wakefulness Test.

[Slide]

These 2 studies, the design of which has been reviewed by Dr. Houghton, again found significant reductions in slow wave sleep, that is to say stage 3-4 sleep or slow wave sleep, and reductions in nocturnal awakenings. Additionally, the Scrima group reported a reduction in stage 1 sleep, a very light stage of sleep, and the Lammers group noted significant reduction in the percentage of time patients spent awake during nocturnal polysomnography.

[Slide]

The most recent study, a multi-center trial performed at 4 sites with an enrollment of 25

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patients, was designed to further explore the effects of sodium oxybate on nocturnal sleep parameters and daytime measures of sleepiness and alertness. In this open-label study patients were

kept at a stable stimulant dose throughout the protocol. Cataplexy medications were tapered, followed by a 2-week washout and baseline period. Sodium oxybate was initiated at 4.5 g in a divided nightly dose for 4 weeks, then increased to 6, then 7.5, then 9 g for 2 weeks each. Nocturnal polysomnography and the Maintenance of Wakefulness Test, or MWT, were obtained at the time points noted here.

[Slide]

This study revealed the expected increase in slow wave, or stages 3-4 sleep, and increase in delta power. Delta power is the measure of the depth of sleep. It incorporates the combination of the amplitude of the slow frequency waves and the prevalence of those waves through the night to produce a single number called delta power. Delta power is another measure found in a variety of animal and human studies to correlate positively with sleep quality. The calculation of this value requires sophisticated processing which was

unavailable for the prior studies. The increments in slow wave sleep and delta power were found to be dose related. Dose-related improvements in daytime alertness and subjective sleepiness were also observed.

[Slide]

The dose-response increase in the number of minutes of slow wave sleep is illustrated in this slide, with an increase from 6 g up to the 9 g dose. The total duration of slow wave sleep increased to over 5-fold that of baseline at the 9 g dose.

It is important to note that while these results are predicted to be dose related, time on medication cannot be factored out as a potential contributor to these increments.

[Slide]

Delta power, which characterizes slow wave activity throughout the entire sleep period, not just during stages 3 and 4, was also found to increase in a dose response fashion with a 50 percent increase noted at the 9 g dose over baseline.

[Slide]

The Maintenance of Wakefulness Test, or

MWT, is a daytime evaluation which places the patient in a dimly lit room in a semi-recumbent position, with nothing to do and with the instruction to remain awake. The duration of sustained wakefulness was measured in this study over 40-minute intervals across 4 periods, spaced 2 hours apart during the day. Substantial dose-related increases in the ability to remain awake were observed at both the 4.5 g and 9 g doses.

[Slide]

As previously noted, the MWT was not performed at the 6 g nor 7.5 g doses in this protocol. Similar marked reductions were found in the Epworth Sleepiness Scale scores. In this measure the individual rates their own potential to fall asleep in a variety of more sedentary daytime activities.

[Slide]

A post hoc analysis of the possible correlations between sodium oxybate-related changes

in nocturnal parameters with changes in daytime measures revealed the strongest correlation occurring with delta power and Epworth Sleepiness Scale scores. This was a negative correlation,

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such that the greater the delta power, the lower the daytime sleepiness. In addition, trends toward significant correlations between delta sleep and MWT scores, and between slow wave sleep and Epworth and MWT scores were observed.

[Slide]

In conclusion, studies of sodium oxybate's effects on sleep demonstrate increases in measures of restorative sleep, including dose-related increments in slow wave and delta sleep, coupled with and correlated with improvements in measures of daytime alertness and sleepiness.

It is postulated that sodium oxybate works directly to enhance brain neurochemical activity critical to the restorative mechanisms of slow wave sleep and of slow wave activity during the total sleep period. Such enhanced activity may be the cause of substantial improvement in both subjective and objective measures of sleepiness and alertness observed with sodium oxybate in narcolepsy.

DR. REARDAN: Thank you, Dr. Black. Dr. Houghton will now present the safety summary overview of Xyrem and finish up with a benefit/risk assessment.

Safety Overview and Summary of

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Risk/Benefit Assessment

DR. HOUGHTON: Thank you.

[Slide]

I am sorry to horrify you with this

complex diagram again but it is just to outline the 15 studies that will be referred to today as the updated safety database. The Lammers study was excluded because adverse events were not recorded in the classical way and, as Dr. Katz explained, the Scharf study was separated and will be explained again later.

[Slide]

The safety profile was reported based on exposure of 479 narcoleptic patients and 125 healthy volunteers from the pharmacokinetic studies. This represents an exposure of greater than 6 months in 360 patients in total, and greater than 12 months in 296 patients, which represents a total patient-year exposure of 1328 years with the Scharf database included.

[Slide]

When exposures were restricted to the studies other than the Scharf database, 399 narcoleptics and 125 subjects represent exposure in 524 persons. This represents exposure of greater

than 6 months in 296 patients and greater than 12 months in 223 patients, for a total exposure of 330 patient-years.

[Slide]

In the open-label studies patients were titrated between the doses of 3-9 g in divided dose at night. This slide represents the distribution of patients across this defined dose range and, again, identifies the 6 g dose as the most commonly used, followed again by the 9 g dose. In fact, approximately 80 percent of patients were titrated within the 6-9 g range.

[Slide]

In the updated integrated safety database, composed of 402 patients, 399 of whom were treated with active drug and 3 patients received placebo only, it can be seen that 65 percent of patients completed therapy or were ongoing in the treatment IND study. Thirty-five percent have discontinued treatment for the reasons noted here, with 13 percent discontinuing due to adverse events; 2 percent discontinuing because of lack of efficacy; and there were 2 deaths that occurred in the treatment IND studies, both due to suicide.

[Slide]

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Across all of these studies, 82 percent of treated patients reported any adverse event, as did 70 percent of patients exposed to placebo. It is important to note that the placebo exposure represents 4 weeks as compared to active drug treatment over a much longer period of up to 4 years. Hence, severe adverse event discontinuations and serious adverse events are significantly greater in the active treatment groups.

[Slide]

When considered in terms of dose at onset, there seemed to be a slight preponderance of incidence in the 9 g group.

[Slide]

This slide represents the most frequent adverse events reported across the integrated database. There was a consistent pattern of events across the study. Nausea, dizziness, sleep walking, are represented here as a partial representation of the term sleep disorder, enuresis

and confusion were most frequently considered dose related, while others represent intercurrent illness.

[Slide]

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This profile is reinforced by consideration of the controlled trials in which there is represented a balanced exposure to placebo and active medication. Again, dizziness, nausea, pain, sleep disorder, confusion, infection, vomiting and urinary incontinence separate. A dose relationship was shown introduction eh GHB-2 trial for confusion, nausea, dizziness and urinary incontinence.

[Slide]

In the SXB-21 trial the most common adverse events that were reported are shown here. The incidence was very low in this study of patients on long-term treatment, but what is relevant is the data that looks at the possible presentation of a withdrawal syndrome with the abrupt cessation of long-term therapy.

[Slide]

This is in marked contrast to a severe syndrome that is being described in the abuser population who have significantly escalated both dose and frequency of dosing. When we looked at symptoms that could relate to a withdrawal phenomenon, we saw only 2 patients with anxiety in a circumstance of escalating cataplexy, 1 patient

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with dizziness, 1 insomnia, 1 sleep disorder that actually in verbatim terms, was increased awakenings, and 1 patient with somnolence as their narcolepsy worsened.

[Slide]

I would like to now address the Scharf database. This was conducted under an investigator IND commencing about 10 years before Orphan's involvement, without any of the rigors of external monitoring, and really represents over 16 years experience in the use of the drug rather than drug development clinical research with regulatory disciplines.

Patients were scattered all over the country and, hence, the data is based primarily on diary recordings without medical review and interpretation, leading to a significant discontinuation rate for lack of compliance. Dose accountability and titration were less clearly defined and less controlled. Patients had less defined entry criteria and represent a broader profile of associated pathologies. On this basis, the study data has been reported separately to the integrated database, as Dr. Katz had suggested.

[Slide]

We will address the Scharf open-label experience in terms of dosing exposure, patient disposition, adverse event incidence over 16 years, and then to try and establish some parity with the integrated database. We have considered the adverse event experience reporting in just the first 6 months of the study.

[Slide]

Patient disposition in the Scharf database is represented in this slide. At the time of database closure 63 patients transferred into the SXB-7 protocol. The FDA expressed concern

regarding the accountability of the 80 patients that did not continue. We provided a narrative account for each individual patient, with updated status where possible, in the form of a major amendment. In addition, FDA requested further clarification of adverse events initially deemed uaevaluable, which we have also provided.

Of these 80 patients, 8 continued in the Scharf trial under his treatment IND. The 71 patients who withdrew had received oxybate for from 5 days to 10 years, and the reasons for early withdrawal of the 71 patients were primarily classified into non-compliance, adverse event and

cost.

[Slide]

The adverse event profile reflects the length of the study. The relatively large numbers of viral infection, flu syndrome, pharyngitis, etc. shouldn't be worrisome considering the 16 years duration of the study. However, of particular interest is the unusual incidence of sleepwalking and urinary incontinence and these will be discussed in some detail later.

[Slide]

The most frequent adverse events in the first 6 months of the Scharf trial are shown here. When compared to the integrated safety database, few adverse events separate in incidence. Most notable are somnolence, infection, viral infection and malaise. There were few new adverse events reported after the first 6 months.

The FDA requested further information regarding the following adverse events of particular interest. They were represented by

incontinence and convulsions, confusion, neuropsychiatric events and sleepwalking.

[Slide]

I will address incontinence first. In

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their review of the GHB-2 trial, submitted in October, 1998, the FDA requested an analysis of adverse event terms for incontinence in association with central nervous system adverse events suggestive of seizure.

[Slide]

We responded by initiating the following: a questionnaire to all investigators to review the history of abnormal nocturnal observations that could be suggestive of seizures; a detailed urologic history preceding oxybate therapy and any new neurologic symptoms.

Examination of the databases for potential correlation between central nervous adverse events that could be related to seizures and incontinence, either urinary or fecal, was undertaken. Review of both preclinical and clinical data in the literature was performed and an overnight EEG recording after a 9 g dose was conducted in 6 patients who had reported incontinence during their oxybate therapy. An expert opinion was provided by Dr. Nathan Chrone, a neurologist of Johns Hopkins University.

[Slide]

The issue as represented is shown here.

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Urinary incontinence was presented by 8 patients reporting 15 events in the GHB-2 study, by 13 patients reporting 51 events over the 2-year period of GHB-3, and in the Scharf study by 33 patients

reporting 140 events.

When central nervous system events were analyzed for contemporaneous reporting, 2 patients in each of the GHB-2 and -3 trials recorded such events corresponding to episodes of incontinence, as did 7 patients in the Scharf database. Relatively few incontinence events were temporally associated with the CNS adverse events suggestive of seizure. No potential seizure genesis was reported by bed partners in response to specific questions, and many of the partners reported relevant urinary symptoms such as frequent nocturia preceding the Xyrem treatment.

[Slide]

Single events of fecal incontinence occurred in 4 patients in 4 different trials. Association between these incontinence events and central nervous system adverse experiences were present only in 1 patient in the Scharf trial and 1 in the pharmacokinetic SXB-11 trial. In this patient the event of fecal incontinence was

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definitely associated with a seizure in a patient with a known pre-study history of seizures. The subject in the SXB-11 effect of food study was a patient who, while significantly obtunded and with respiratory obstructive symptoms, had a brief episode of fecal incontinence.

[Slide]

In conclusion, there was limited support for a relationship between incontinence and seizures from the clinical trials, the prospective EEGs or from the literature.

[Slide]

The vast majority of events that could have been coded as convulsions were actually recorded under the COSTART dictionary as cataplexy events. One patient in the integrated trial database did not represent this classification and he has been investigated by a neurologist for seizure genesis. His fugue state and automatic behavior episodes have been deemed part of his narcolepsy syndrome.

In the Scharf database two patients with definite seizures recorded history of preexisting disease, and two other patients recorded seizure events without definitive diagnosis but with

complicated polypharmacy.

[Slide]

To now address confusion, in the integrated safety database 30 patients or 70 percent reported 48 events recorded as confusion, leading to discontinuation from study in 3 patients. A possible dose relationship was suggested by a review of the entire database. In the Scharf database, again 7 percent of patients reported 15 such events, with no discontinuations and no dose relationship pattern observed.

[Slide]

The coding of confusion embodied a wide range of verbatim terms, as shown here. These do not represent confusion based on a standard medical status examination. They do not differentiate between nighttime events from those of awakening or arousal parasomnias. These events led to no dosage adjustment in 37 instances, but dose was reduced in 4 events, led to temporary discontinuation following 4 events, and 3 patients discontinued

permanently because of a side effect of confusion.

[Slide]

When the GHB-2 controlled trial was considered with respect to confusion, the highest

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incidence in the databases is represented in this 4-week study by 10 patients. The highest incidence was seen in the 9 g dose, and 6 of the 10 developed during the first week of treatment. Seven of these 10 events were in patients over the age of 50. The difference in this study, of course, was the assigned doses rather than dose titration. It is important to note that 1 event was reported in a placebo patient.

[Slide]

In conclusion, the term represents a symptom report rather than confusion defined in a medical sense by formal mental status examination, and all resolved usually without interruption of therapy or dose modification. Confusion and other associated symptoms are not unexpected with sedating medications. The blinded, controlled trial results suggest that a higher incidence may result without dose titration.

[Slide]

Neuropsychiatric events will now be reviewed. The adverse event database was searched for terms that could represent neuropsychiatric symptoms, and this led to the classification shown in this slide. Fifty-two patients reported 57 such

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events in the integrated safety database, of whom 12 discontinued as a result of these events. In the Scharf database 41 patients reported 84 such events, leading to 2 patient discontinuations.

[Slide]

Of these 57 events, 1 occurred while a patient was on placebo. This slide lists the terms examined and some, such as stupor and coma, failed to represent neuropsychiatric events. Many represented symptoms of narcolepsy such as hypnagogic hallucinations COSTART-coded to the term hallucinations. The most frequent was clinical depression, and this represents a symptom rather than a diagnosis of major depressive disorder. Depressive symptoms are frequent accompaniments in narcolepsy, and this is well recorded in the literature. Suicide was attempted in 4 patients with major preexisting psychiatric history, and resulted in death in 2 of these patients. The other representations of psychotic disorders and the patient with manic depressive disorder also occurred in patients with preexisting major psychiatric disease. As is shown, a similar profile of reported symptoms is found in the Scharf database.

[Slide]

In conclusion, most patients with major events had a preexisting psychiatric disorder. Many events do not qualify as neuropsychiatric disorders, as was represented by the terms pointed out. Assignment of causality is very difficult because narcolepsy is associated with depression and even mechanistically there has been an association between psychosis and the central processes in narcolepsy. As Dr. Mignot mentioned, stimulant medications are associated with central nervous system side effects that are represented by

neuropsychiatric symptoms. And, it is true to say that in many patients, particularly in the Scharf database, pre-study screenings were deficient.

[Slide]

To lastly address sleepwalking, in the integrated safety database 7 percent of patients reported such events, whereas in the Scharf database 32 percent of patients reported events that were listed as sleepwalking. In the Scharf trial, however, these reports were primarily data listings in patient diaries in response to a specific leading question, listed as a line item in the diary.

[Slide]

The listing of this term did not receive the benefit of medical consideration of a differential diagnosis of somnambulism, and since most patients were not seen by the investigator no clarification was provided. Post hoc consideration was rendered impossible given the lack of information regarding sleep stage, time of night, relationship to drug dosing, and could be representative of any of the differential diagnoses listed on this slide.

[Slide]

In the controlled trials only 3 sleepwalking events were reported, 2 of which occurred on active treatment and 1 occurred in a patient during placebo treatment.

[Slide]

Hence, in conclusion, the incidence in the integrated safety database of 7 percent is not particularly dissimilar to the range reported in the literature for normal patients. This was

reported by Dr. Mahowald, of Minneapolis, as between 4-10 percent in a publication in 1998, and between 1-7 percent by Dr. Roger Broughton of Canada.

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Diary recording without medical classification represents a potential increased reporting in the Scharf trial. The slight increase in incidence over the general population may certainly be representative of Xyrem effects with increase in slow wave sleep, but REM behavior disorder, common in narcolepsy, mayou be a separate consideration.

[Slide]

To summarize the safety profile of this drug, we based our assessment to date on 604 patients, which represents 524 patients excluding the Scharf database. Dosing was between 3-9 g per day in divided nightly dosing. The common adverse events were certainly headache, unspecified pain, nausea, dizziness, and less common but important adverse events were vomiting, confusion, restlessness, agitation, sleepwalking and enuresis.

[Slide]

All events have been reversible. There were no significant changes in lab values or vital signs identified across the studies. There was no evidence of organ toxicity outside the pharmacologic effects in the central nervous system. There was no diversion or consumption of

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clinical trial supplies by any family members during the trials, and there was certainly no evidence of Xyrem diversion in our database.

[Slide]

I would like to conclude with the statement that Xyrem was generally well tolerated.

[Slide]

To commence a risk/benefit assessment, I would like to remind you of the indication proposed by Orphan Medical for the use of Xyrem. That is, to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

[Slide]

As has been pointed out, narcolepsy is an uncommon disease, with an incidence of around 0.05 percent and, as such, has been qualified for orphan designation. There are no therapies approved for the treatment of cataplexy. Because of this, the FDA were very kind to apply a priority review to our submission and we are very appreciative of that recognition. Current off-label therapies, so well described by Dr. Mignot, are unsatisfactory. Excessive daytime sleepiness has approved therapies but these do not address cataplexy. There is

clearly a medical need existing beyond the therapies available.

[Slide]

The benefits of Xyrem in the trials presented were based on patient diary recordings, investigator ratings of overall clinical improvement in overall disease severity, and objective measures of changes in sleep architecture and daytime response.

[Slide]

Clinical benefit in the short-term reduction in cataplexy was shown by the

dose-related reduction in cataplexy in the GHB-2 and Scrima studies and in the long-term efficacy in the SXB-21. Subjective changes in the Epworth Sleepiness Scale have been well demonstrated, and reduction in daytime sleep attacks have accompanied this change. Early objective Maintenance of Wakefulness Test data supported these changes in daytime sleepiness. The global impression of the investigators for overall changes in disease severity also showed a significant dose relationship.

[Slide]

Xyrem was generally well tolerated when

used in the proposed dose range, with the most common side effects reported including nausea, dizziness, headaches, pain and confusion. Less common but important associated effects include enuresis and sleepwalking, with a possible dose relationship suggested. Although there were 11 deaths in the Scharf trial over 16 years and 2 deaths by suicide in the integrated database, no deaths were associated with Xyrem.

[Slide]

In relation to the specific FDA inquiries, there is a possible relationship between Xyrem therapy and somnambulism but further definition is required. There is a marked discrepancy between the reported incidence in the Scharf study of the 32 percent, recorded solely by diary entry in response to a leading question, and the 7 percent in the integrated database, which is really in the range in public literature for the normal population. In the controlled trials there were only 3 such reports in total, 2 recorded in active

treatment and 1 during placebo treatment.

[Slide]

Confusion is also an adverse accompaniment of sedative hypnotic drugs and has been identified

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as an occasional side effect of Xyrem. Dose titration may assist in limiting this side effect but it remains an important component of patient and physician education.

[Slide]

The incidence of enuresis with Xyrem treatment supports an association that may be dose related, but any association of these events with seizure activity is very weak. In terms of Xyrem causing seizures at the therapeutic doses, there was no reliable support for such causality. In this regard, the coding to the COSTART dictionary terms of cataplexy as convulsion was confusing. However, there were 2 patients recording seizures with preexisting causes. Two further patients in the Scharf database reported seizures where confounding contributions rendered assignment very difficult. One patient in the Orphan studies represented a complex history of symptoms characterized by fugue state and these symptoms have been attributed to his narcolepsy syndrome.

[Slide]

No significant measures were seen in laboratory measures, vital signs or ECG measures and these changes were comparable across the

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treatment groups. There was no evidence of organ toxicity at therapeutic doses that were not part of the central nervous system pharmacology of the drug.

[Slide]

We did not identify any evidence of kinetic or dynamic tolerance in the narcoleptic populations studied and the absence of drug-drug interactions in the 3 classes of drugs commonly used in narcolepsy, along with the absence of either induction or inhibition of the oxybate p450 enzyme system make it possible to predict that drug-drug interactions should be minimal.

[Slide]

Although a serious withdrawal syndrome has been described in the abuser population that relates to escalation in both dose and frequency of dosing, no evidence of withdrawal has been demonstrated in patients maintained on long-term therapeutic doses in narcolepsy. Following abrupt discontinuation of long-term dosing in the blinded study, only 2 patients reported anxiety but in the presence of worsening cataplexy, with 1 patient reporting mild dizziness and 1 report of insomnia.

[Slide]

We have not attempted in any way to minimize the issue of abuse with GHB or its precursors. We recognize that this is a serious problem, but stress the fact that this has been peripheral to the development program in narcolepsy. We have detected no evidence of abuse, diversion or self-escalation of dosing in patients in clinical trials. Great efforts have been applied to working with the appropriate expert bodies to plan a restricted distribution system to support in every way the unique bifurcated scheduling legislated by Congress and to plan

physician and patient education to minimize the possibility of diversion. This will be greatly facilitated by the documentation centrally of prescribing and patient use. This will be described in detail to you later.

[Slide]

In conclusion, I would propose that we have established statistically and clinically significant evidence for the reduction in cataplexy, and for improvement in daytime sleepiness when used concomitantly with stimulant medications.

Xyrem is generally well tolerated, with a

safety profile well characterized in this orphan population by long-term exposure. The medical benefits clearly outweigh the risks for a therapeutic agent that may be the first single agent to address the multiple symptoms of narcolepsy. Thank you very much.

DR. REARDAN: I would just like to thank the committee and FDA for your attention. I believe Dr. Mani has some comments, or we are now happy to take questions from the committee.

DR. KAWAS: The FDA will give us a response to the presentation, and then we will probably take a break before we have questions, unless the committee has anything burning they need to ask now. Dr. Ranjit Mani will present for the FDA.

FDA Response to the Presentation

DR. MANI: What I propose to do in the next few minutes is address two issues where our views diverge somewhat from those of the sponsor.

[Slide]

The first is the effect of GHB on measures of daytime sleepiness in narcolepsy.

[Slide]

This overhead illustrates how many

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measures of daytime sleepiness there were in the GHB efficacy trials. As you can see, GHB-2 had 3 measures of daytime sleepiness; the Scrima study had 2, of which 1 was primary; and the Lammers study had 2. I will draw your attention to the fact that, with the exception of the Scrima study, the remaining measures were all designated as being secondary.

[Slide]

Because what is considered statistically significant does depend or could depend on the number of comparisons made, I think it is also important to illustrate how many secondary efficacy measures there were in each trial. In the GHB-2 trial I was able to count a total of 10; in the Scrima study 17; and in the Lammers study 7.

[Slide]

This is based on data provided by Orphan. As you can see, in the GHB-2 trial the Epworth Sleepiness Scale measure did reveal a fairly clear-but efficacy for GHB but only at the 9 g dose. The p value of 0.001 probably remains statistically significant even when adjustment is made for multiple comparisons.

On the other hand, the frequency of

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daytime sleep attacks and duration of daytime sleep attacks should probably be considered negative evidence of efficacy if adjustment is made for multiple comparisons.

[Slide]

Again, in the Scrima study one primary efficacy measure was sleepiness index of the Multiple Sleep Latency Test. Here, the results must be considered negative whether adjusted for multiple comparisons or not.

[Slide]

The other measure was the frequency of daytime sleep attacks, again negative whether adjusted for multiple comparisons or not.

[Slide]

In the Lammers study the severity of daytime sleepiness was 1 of 7 secondary efficacy measures which is probably negative when adjusted for multiple comparisons. On the other hand, the frequency of daytime sleep attacks was positive, but using an ANCOVA which was not a protocol specified analysis.

[Slide]

So, here are the problems as we see them with the proposed claim for excessive daytime

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sleepiness. Most measures were secondary. The only measure that was primary was negative. The majority of measures were negative after adjustment of the Type 1 error for multiple comparisons. The effects were inconsistent across studies, and the clearly positive results on the GHB-2 trial on the Epworth Sleepiness Scale were not replicated. As mentioned, the approval of modafinil for the treatment of excessive daytime sleepiness was based on replicated results in 2 efficacy studies. And a minor point, the results on the GHB-2 study were, to some extent, confounded by concurrent stimulant

use, raising the question, among other questions, of whether Xyrem is effective as monotherapy for the treatment of excessive daytime sleepiness.

[Slide]

The second issue that I want to address briefly is that of sleepwalking. As you can see, I have put it in quotes. As Bill Houghton has already emphasized, we do not know what these episodes represent. They have not been clinically characterized.

[Slide]

The term sleepwalking does not correspond to the medical entity of somnambulism. The term is

based entirely on patient diary entries, and there has been no attempt to characterize the episodes further and define what clinical entity they correspond to.

The incidence of these episodes, whatever they may represent, was approximately 32 percent. The majority of patients did list as having more than one episode. A single patient had a total of 346 episodes over a 5-year period. As already said, an adequate clinical description is lacking, and the episodes cannot be said to be completely benign.

There was one patient who is reported to have overdosed twice during two consecutive episodes of sleepwalking. During one episode the patient became comatose and needed to be hospitalized, needed to be on a ventilator for some hours but completely recovered. A second pat had multiple episodes of sleepwalking. She was found by her husband to be smoking, apparently inadvertently. During one such episode her clothes

were set on fire. The fire was put out. She was taken off GHB and did not have any further such episodes. A third patient is reported to have swallowed nail polish remover during an episode,

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without any serious consequences.

I would also like to add one minor point in response to Dr. Houghton's presentation. That is, I believe that in the Scharf study there was one patient who was withdrawn from the study because he felt that he had benefitted from Xyrem and decided that these benefits could be extended to a circle of friends who also received part of his own supply, again apparently without serious consequences. Thank you. That is really all I have to say.

DR. KAWAS: Thank you, Dr. Mani. Does the committee have any questions they would like to ask before the break? If not, we will reconvene this meeting at 10:30 sharp.

[Brief recess]

Committee Discussion

DR. KAWAS: Will you please have a seat so we can reconvene this session? This meeting of the Peripheral and Central Nervous System Advisory Committee is now reconvened. We appreciate the presentations from the sponsor and the FDA, and the floor is open for questions. The first question is going to come from someone who has been patiently sitting on the phone. Dr. Chervin, can you hear

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me?

DR. CHERVIN: Yes, thank you.

DR. KAWAS: Dr. Chervin, we can't year you yet, if you will give us a moment to do whatever it

is we have to do?

DR. CHERVIN: Can you hear me now?

DR. KAWAS: Give it a shot.

DR. CHERVIN: I have a question perhaps for Dr. Houghton. In regard to the safety experience with the 1328 patient years, were there any reports that alcohol was taken in the evening in combination with GHB? If so, what was the outcome?

DR. HOUGHTON: It was certainly recommended as a contraindication in our protocols. The advice to the patient was that they not consume alcohol during the studies. I can't vouch for the fact that it was entirely complied with, but we don't have protocol or database record of consumption of alcohol during the trials. There certainly is record of patients having imbibed during the Scharf study and I am not in a position to clarify that.

DR. GUILLEMINAULT: This is Dr. Guilleminault. I have also a question, and it is

for Dr. Mani, about the sleepiness data. Was there the slow wave sleep information looked at for sleepiness? As you know, delta power greatly improves alertness and there are many studies, sleep deprivation studies and investigation into sleep disorders such as obstructive sleep apnea, where it is very clear that decrease in delta power and in slow wave sleep has a big impact on the alertness, and the more delta power you have and the more slow wave sleep you have, the better alertness the next day.

So, one of my understandings is that this

drug has an impact on slow wave sleep and delta power. Was there any analysis of that in data looking at alertness?

DR. MANI: To the best of my knowledge, it was not listed as an efficacy measure in any of the controlled studies that I looked at.

DR. GUILLEMINAULT: Okay. The second question is maybe a question about my ignorance. I did not understand exactly the statistic about the ESS because in the investigation of the results of the ESS there was an investigation with negative studies. All the results, when you look at everything there, was there a positive p value?

Was there a statistical difference? Because I don't understand the manipulation which was done. Maybe through poor knowledge, I have never seen this type of manipulation.

DR. REARDAN: Dr. Guilleminault, which study are you referring to when you ask about the Epworth Sleepiness score?

DR. GUILLEMINAULT: I think OMS-2.

DR. REARDAN: Is that for Dr. Mani, or do you want to pose that to the company?

DR. GUILLEMINAULT: No, I was asking that because Dr. Mani reported that he looked at that study and classified the results, and my understanding, and it may be a wrong understanding, is that he made a subdivision in looking at the results and I did not see completely the statistical rationale for that approach.

DR. MANI: Are you referring to the statistical adjustments for multiple comparisons? Is that what you mean?

DR. GUILLEMINAULT: No, the Epworth

Sleepiness Scale study in GHB-2, secondary efficacy daytime sleepiness on your slide, and I did not understand exactly how that was analyzed, the type of analysis that was done or redone.

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DR. MANI: Perhaps I should ask the Orphan statisticians to explain that in greater detail, but the analysis was an ANCOVA.

DR. GUILLEMINAULT: The microphone must be poorly placed because we cannot hear the response.

DR. MANI: Can you hear me now?

DR. GUILLEMINAULT: Yes.

DR. MANI: The analysis was an ANCOVA. I mean, perhaps I should get the Orphan study statistician to explain the analysis to you in greater detail.

DR. REARDAN: I am just asking Dr. Richard Trout, the statistician, to comment on how the Epworth Sleepiness score was statistically analyzed.

DR. TROUT: Hi. My name is Dick Trout. First of all, the analysis was just as you described, that is to say it was an analysis of covariance which was preplanned. I think the concern that you expressed was the fact that it was listed as a secondary efficacy measure --

DR. GUILLEMINAULT: Right.

DR. TROUT: -- as compared to a primary, and there was a number of secondary efficacy measures, but even if one adjusted for the multiple

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testing which I think you were concerned about, the 9 g separation from the placebo group would still be significant. We already adjusted for the multiple testing with regard to the dosing issue,

using Dunnett's test, but your concern was with regard to the fact that there were a number of secondary efficacy measures which would then diminish the effect.

DR. GUILLEMINAULT: Okay, thank you.

DR. PENN: I can see that the claim for helping daytime sleepiness is going to be one that we will want to look into very carefully, and I want to ask our FDA statistician a question about that in a general sort of way. If you were a gambling person, which I assume a statistician would not be --

[Laughter]

-- from the data that you have looked at for 9 g, would you say that in a good controlled trial you would bet on it working to decrease daytime sleepiness? It looks like the strongest data is at 9 g and that is what the company is suggesting. I am going to ask you to bet on that, and then I am going to make a point.

DR. MANI: You addressed the question to a

statistician; I am not a statistician.

DR. PENN: Oh, I am sorry. Anybody else want to gamble with this?

DR. REARDAN: Coming up to the podium is Dr. Sharon Yan, who is the FDA statistician that has been working on the Xyrem program.

DR. YAN: Basically we rely on the results that were prespecified, and a lot of results that we looked at -- and you want me to bet -- after looking at those results, most people would bet that the data shown, for example, the 9 g it seems that it is highly positive; it is highly

significant, but we rely on the analysis which is prespecified. Without that, the data information -- it is hard to bet on anything.

DR. PENN: But I am asking you how you would bet on that if you had to make a bet now in Las Vegas, and the point I am trying to make is that it seems to me a reasonable bet that it does help daytime sleepiness but that they haven't presented two clean studies that show at 9 g that that is the case. And, is there going to be some middle ground to this where that claim can be put in language that would be acceptable later on? So, I wanted to see if you agree that that analysis

then presenting of the problem is the correct one, that is, that there is very strong suggestive evidence, not as strong as we often want for a claim, that it helps daytime sleepiness. When you sit back and you look at all the data, would you bet on that helping daytime sleepiness?

DR. KAWAS: Perhaps Dr. Katz could help with this response.

DR. KATZ: Yes, again, I will just sort of reiterate something that Dr. Yan has already said, which is that whether or not we personally believe something is true or what we would bet on is not really the standard. The standard which we apply is what the law requires, which is substantial evidence of effectiveness, ordinarily defined, unless there is some compelling reason to do otherwise, as data from at least two adequate and well-controlled trials demonstrating effect. We have adopted by tradition a usual sort of statistical rule by which we decide whether or not a study is "positive" for a particular indication.

So, I think that is the standard. Unless there is some, as I say, very compelling reason to apply some different standard, like what would I bet on or what my personal belief is, that is the standard we need to apply. Again, unless there is a view that there is some compelling reason to apply some different standard, we would ask you as a committee whether you think that the evidence for that particular claim meets that standard.

DR. PENN: So, once again the question should go then to Orphan, whether or not they feel they have met that standard on two separate occasions using their 9 g amount, and I haven't gotten a clear-cut idea in my mind whether they are really claiming that or just showing us data that would be for a good bet.

DR. YAN: May I clarify one thing? For the analysis for daytime sleepiness for GHB-2 the sponsor showed it was highly significant, with a p value of 0.001, and I analyzed the data with the original scale and, as I analyzed it, it shows that the normal assumption was validated and then the log transformation to then improve the data, and I used nonparametric analysis to analyze the p value, and it is not that small. As I remember, the p value is 0.03 or something.

DR. REARDAN: I can comment on the trials. We have GHB-2, obviously, where the trial was very effective. I don't think there is a dispute with FDA on that. The question is do we meet the standard of two well-controlled trials for that indication. The data in support of that comes from the Lammers study. The sleepiness scale used there

was something he developed, not a validated scale but it was statistically significant for daytime sleepiness, albeit in a very small, 24-patient crossover trial.

So, we have a small supportive study. We have the large controlled study, GHB-2. That is the evidence basically. Bill, do you want to comment?

DR. HOUGHTON: Yes. We are not trying to make this something that it is not in any way, and if you apply the absolute, most rigorous standards of normal drug development to our database, we have a small database. We did have the two components that were statistically significant. This was supported by the reduction in daytime sleep attacks which are very clinically significant to the patient, and we had two components of statistical significance there.

The other issue, and I know that this from a pure mathematical sense is problematic, is the evidence of long-term support in daytime sleepiness

claim with the GHB-3 protocol, which showed the Epworth Sleepiness Scale and the daytime sleepiness reduced and maintained over the long period of time. The fact then that the objective data in SXB-20 was so strongly supportive and the change in Maintenance of Wakefulness Test is an objective measure and was clearly positive was very important.

The part that concerns me from a clinical point of view is if you look at the patient profiles as they enter the studies, they are on stable doses of stimulants and, yet, their ratings

are very low. The real issue is that daytime sleepiness with current medications isn't well addressed. So, the question is not only have we shown absolute irrevocable evidence of long-term efficacy for daytime sleepiness with the existence of the present treatments for long-term effectiveness, what we didn't do is ask for a claim in daytime sleepiness.

[Slide]

Our proposed indication was to improve the symptom. We didn't attempt to do studies that displaced the stimulant therapies. What we are really looking at is a hand-in-glove approach that

actually makes patients better as an incremental change, and all therapies up to now have been very separate. The symptoms of daytime sleepiness and those of the associated REM phenomena have been treated by entirely separate medications. If there is a component of Xyrem that assists in daytime sleepiness as an incremental change, we think it is very clinically important and that is what we sought to present today. I want to stress very clearly that we are not looking for the claim of daytime sleepiness; we are looking at an improvement in the symptom thereof.

DR. KAWAS: Dr. Houghton, can I ask you then, to my reading, that indication is actually two indications, I mean, cataplexy and sleepiness being a separate one. When I was reading the materials that you very carefully provided us, obviously for cataplexy the GHB-2 and the SXB-21 study speak to that issue as pivotal trials. I was going to ask you which were the two that speak to the issue of daytime sleepiness. Now I understand

them to be the GHB-2 and the Lammers small trial with the questionnaire that was developed there. In both of those cases, however, we are talking about subjective sleepiness from the Epworth scale

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and the other question. Since there are factors that can influence someone's subjective feelings of sleepiness, do you have any objective measures that support the indication of daytime sleepiness? Specifically, the one trial that I am aware of that had an MSLT and did daytime sleepiness as a primary outcome measure, in fact, appears to be not supportive of the indication.

DR. HOUGHTON: Yes, in the Scrima trial he used the MSLT measure and that was not statistically significant, as shown. The objective data that we propose supports very strongly the effect of adequate dosing of GHB was the SXB-20 trial that Dr. Black discussed. That is not only a profound improvement in the MWT at the 9 g dose but a defined dose response across all doses. That is very positive data.

DR. KAWAS: In ten patients, it appears.

DR. HOUGHTON: Twenty-one.

DR. MANI: May I also add that that was an open-label, non-randomized study?

DR. HOUGHTON: Sure, but using an objective measure.

DR. RISTANOVIC: I am I am Ruzica Ristanovic, medical director of Sleep Disorders

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Center, in Evanston, Illinois. I would like to comment on add-on Xyrem in the presence of other stimulants. Other studies attempt to try to document the effectiveness of other stimulants in

narcolepsy-related sleepiness documents, including the most rigorous trial of modafinil in double-blind, placebo-controlled studies. They document that these drugs improve sleepiness but very seldom outside of the range of pathological sleepiness as measured by Multiple Sleep Latency Test and Maintenance Wakefulness Test. So, the patients remain sleepy. That is the message. Add-on treatments are approved for other indications in other neurological diseases, such as epilepsy. So, I assume that this application for that particular indication is not for monotherapy but as an add-on to concurrent use of stimulants. I would like to bring this to your attention. So, patients do remain sleepy on stimulants and they need additional treatments.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: Dr. Houghton also seemed to be distinguishing between monotherapy and add-on therapy. That is not the problem. The problem is whether there is adequate support for use as an

addition for whatever else the patient is on, and whether there are well-controlled studies that support that. So, add-on would be perfectly fine. That is usually true in a lot of conditions, not just neurological ones, where you continue to give standard therapy and try to improve it.

I just want to make one observation about the evidence. We do expect to see replicated or reproduced findings. Some of the issues here are whether the fact that the endpoints are secondary and need some correction means that there isn't adequate support. A lot of these things are

matters of judgment that the committee can weigh in on. Not everything is, you know, a yes/no. Some of the things are moderately subtle and that is why this is being brought to you for judgment. There is one study that is obviously stronger than the rest but the others can be considered, and you sort of have to think about how many real endpoints there really are; how much of a correction is needed. Those are difficult discussions but worth considering.

DR. KAWAS: Dr. Katz?

DR. KATZ: I agree, but I think we would still have to have the application meet the

standard of independent replication, in other words two trials. You can decide that one of the other trials actually does meet the usual standard, again, taking into consideration the multiplicity and that sort of thing. All I am saying is that I don't think we can say we have one study that looks good. If you believe that GHB looks good and the others sort of contribute to a feeling that it probably is okay, I mean, we really need two independent sources that you believe demonstrate the effectiveness.

The only other point I wanted to add is to something, Claudia, you said which has to do with Dr. Houghton's view that they are not going for a claim of daytime sleepiness; they just want, I guess, to have language in the labeling that says that it improves that symptom. Most of the drugs we approve are for symptomatic claims, so there is no question that the inclusion of this language in the indication is a claim as we always understand that term.

DR. KAWAS: Dr. Guilleminault, followed by Dr. Wolinsky, please.

DR. GUILLEMINAULT: If you look at all the published data on modafinil, on amphetamine, on

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methylphenidate, none of these drugs ever normalized all the objective tests on alertness and daytime sleepiness. None of them, including the modafinil data which were approved by the FDA. The MSLT and MWT for all these drugs are pitiful. The only data which shows significance was the Epworth Sleepiness Scale, which is a subjective scale, in all these trials. So, we cannot expect to have any positive result with subjective tests in any of these drugs. We will always have to rely on subjective tests even if the subjective test is not great. Everybody in the field agrees that the Epworth Sleepiness Scale is the most used scale despite the fact that it has a lot of downfall, and we have to remember that when we look at what has been approved and what is being used.

DR. KAWAS: Thank you, Dr. Guilleminault. I think that many people would agree with those comments, but my question to you would be not whether or not the Epworth Scale subjective measurements are good but do we have two randomized, controlled trials that show an improvement in subjective sleepiness.

DR. GUILLEMINAULT: That was my initial question because my understanding is, when the

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statistician from the FDA responded, she said that when she did a nonparametric analysis she found out that she had a p value of 0.03. So, my understanding is that she had a significant finding

even when she did the reanalysis. That was my understanding of her response.

DR. KAWAS: Would you like to comment, Dr. Yan?

DR. YAN: I am sorry, the previous number is not right. I checked. The number for the nonparametric analysis, the p value was 0.0109.

DR. WOLINSKY: I have a couple of questions first for some information before I ask the real question. For the informational questions perhaps Dr. Mignot could help with. So, the first question I have is if you could enlighten us or re-enlighten us about how many patients that have narcolepsy have had cataplexy as a component symptom. What proportion?

DR. MIGNOT: In most case series it is about 70 percent.

DR. WOLINSKY: The second question is that at least for most of these studies which were done and presented to us since cataplexy was being measured, as is appropriate, the number of

cataplectic attacks was relatively high. I think in these studies it was around 20 cataplectic attacks per week. So, how many of the 70, 75 percent of patients with narcolepsy who have cataplexy have cataplectic attacks at that level?

DR. MIGNOT: I would guess 20 percent.

DR. WOLINSKY: Thank you very much.

DR. MIGNOT: Yes, roughly.

DR. WOLINSKY: And then they would fall down below that level for the remainder of the 55 percent of narcoleptics with cataplectic attacks.

DR. MIGNOT: If you analyze the spread of

the number of cataplexy episodes per week, but you have to balance that also with the efficacy of current treatments. A lot of people that currently have cataplexy that is relatively mild just don't want to take the antidepressants because they have so many side effects, especially sexual side effects, dry mouth, all these problems --

DR. WOLINSKY: This is not the question though. So, now the question to Orphan which has really, truly become an orphan drug question, is since all of the studies that have been done have enriched for cataplexy, do we have any data that would suggest that if cataplexy is adequately

controlled or if there is no cataplexy so we don't have to worry about the control of cataplexy there would be any effect of the drug on daytime sleepiness in non-cataplectic narcoleptics?

DR. REARDAN: I think Jed Black wants to make a comment on that.

DR. BLACK: Just a comment on the prevalence of cataplexy in the 70-75 percent of folks with narcolepsy that had cataplexy, the frequency of events -- this is something that Dr. Mignot is not aware of, the cataplexy was subdivided into major events and minor events. About 20 percent or so would have the major events to that level, but when we look at the minor events a far greater percentage of that 70 percent, which may be up to 80, 90 percent of that 70 percent, will have that number of minor effects. Those are not complete attacks where they fall down. In fact, with most narcoleptic patients, they distinguish between the two and they will often only report to the physician the major events. But

in the diaries that Orphan had set up all the events are characterized.

DR. WOLINSKY: So, the second question --

DR. BLACK: We have no idea. That is an excellent question that I think needs to be determined, but in the studies that have been completed that question cannot be answered.

DR. REARDAN: Jed, the only study I can think of maybe is SXB-20 where cataplexy was not an entry criterion and I don't know what the cataplexy incidence in that trial was. Bill is shaking his head -- we didn't record it and we didn't quantitate it.

DR. BLACK: We can't comment on that.

DR. REARDAN: It is true that in most of our studies patients were selected because at entry criteria they had to have a baseline cataplexy.

DR. KAWAS: Dr. Penix?

DR. PENIX: Before we address the two separate indications issue -- and I guess, Dr. Black, I could direct this question to you -- in the GHB-2 study you did look at all cataplexy events, I guess, and then total and partial cataplexy. In the background material, in the separation of the two it appeared that there was no significant difference in any of the three doses of GHB on total or complete cataplexy but your effect was primarily in partial cataplexy. Is that correct?

[No verbal response]

So, my question in that regard is what is the clinical significance of partial cataplexy, and you mentioned that patients frequently do not want

treatment for partial cataplexy. So, is this a big problem? I presume that the patients that would perceive a problem would be the ones with the complete cataplexy but there we see no significant difference. So, is there a problem there with that?

DR. BLACK: I think this is a good point, and the difficulty comes in trying to separate the two because it is not sort of a box of partial and a box of complete; it is a gradation, you know, ranging from small partials to large partials and the completes. So, I think this analysis is difficult to perform. Clinically the degree of improvement with traditional anticataplectic medications that we use is similar. So, the reduction in partial -- if that is all that is being seen here and I am not convinced that clinically that is the case -- while the statistical analysis didn't demonstrate a significant difference in the complete cataplexy attacks, clinically there is an improvement in all

the different categories, and it is very substantial in traditional anticataplectic medications as well as with GHB.

DR. PENIX: Could Dr. Mignot comment on the clinical significance of partial cataplexy? Is it a big problem?

DR. MIGNOT: Yes, it is a big problem. In fact, the problem is especially the social aspect of cataplexy, when you have to realize that you are just in the middle of a crowd and are meeting some friends, and you can never tell when it is going to happen. It may happen in very odd circumstances.

So, often even the doctors don't know what it is and they just look at it and they wonder why this person is kind of losing slight control and has to sit down. There is also almost a social aspect with fear of cataplexy that can occur at any time, any moment and, yes, it is a very significant problem.

Again, it is a balancing act because the drugs that we use are somewhat effective but they have all these side effects and you just have to choose between two evils. I am pretty sure that, for example, GHB, based on my relatively limited experience, has less side effects than

anticataplectic classical tricyclic antidepressants, and that a lot of patients would prefer to take GHB even for partial cataplexy.

DR. PENIX: The case that you showed of the nine-year child I assume is complete cataplexy --

DR. MIGNOT: Yes.

DR. PENIX: -- but you are also saying that patients with partial cataplexy have a significant impairment of their life.

DR. MIGNOT: Absolutely. But, as Dr. Black mentioned, it is not an "all or none." I mean, most patients, the ones that are complete, have a lot of partial cataplexy. You never know how bad it is going to be. Most of them are small, little attacks, and sometimes they may even be perceived only by the patient. Sometimes the face may melt; the head drops. Sometimes they just have to sit down; sometimes they don't have to sit down. I showed a young kid because it is more dramatic, but you would see the same thing in some of the

patients with partial cataplexy occasionally.

DR. BLACK: I am realizing that a definition may be useful here. In general when we were describing patients who documented the partial

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versus complete, we told them to think about complete as an episode where they fall to the ground with complete paralysis or where, if they weren't sitting, they would have fallen to the ground with complete paralysis. Otherwise, anything else is partial -- so, slurred speech, head drops, dropping things are the partials, and those become very important for quality of life and daytime performance. Driving, those kinds of things can become a very significant event for partials.

DR. MIGNOT: Yes, one thing I should also emphasize is that in a very large number of series that, for example, have analyzed several hundred patients with narcolepsy and cataplexy, as a mean the large majority of patients have several attacks per day, several attacks per week. Between several attacks per day and several attacks per week, that is generally partial or complete attacks and it is not something that appears just once, you know, every ten years. It is really something that occurs regularly and sometimes totally unexpectedly.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: That leads me to a question just for clarification. For the purposes of these clinical trials, were the cataplectic events something that was just perceived by the patient and recorded in a diary, or were they

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verified by some third party?

DR. REARDAN: These were taken from patient diaries. So, it is patient recorded episodes.

DR. HAGAMAN: I am Dr. Hagaman and I just wanted to address the partial versus the complete cataplectic events. I think that you have to take it on an individual basis. We have patients that come in that are teenagers that have tests in front of them and they have a partial cataplectic event and they drop their pencil; people that cut hair that have scissors in their hands and they drop their scissors. So, even though they have not had a complete event, this has been a very debilitating event in their lives. So, it is a continuum and I think you just have to really look at each person as an individual and what they are doing.

DR. KAWAS: Dr. Dyer?

DR. DYER: How variable in the same patients are the number of cataplectic attacks per week? What is the variance in that?

DR. MIGNOT: We have looked at that quite a bit.

Actually, I did some diaries in a large number of patients with cataplexy. It is really totally unpredictable and that is one of the most scary parts about cataplexy when you have narcolepsy. Of course, if something emotional is going to happen, say a patient is going to go to a wedding, often they will kind of fear that event much more because they think it is very likely that they are going to have cataplexy in front of everyone and, indeed, they may actually have a lot more cataplexy because

it is an emotional event.

Still, I have followed, for example, patients and sometimes they may have like 80 for one week and then the following week they may have only three or four. I mean, it can really vary quite a bit. And, one of the main reasons is really that emotion is something that is very variable. In fact, someone mentioned how easy it is to observe cataplexy. It is very difficult to get it on tape because typically the patient come to your office; he really wants to show you what it is but, you know, he is tense and it just will not occur but as soon as he leaves the office and

something happens -- boom, he is going to collapse. So, it is very difficult to predict and it is quite variable.

DR. ROMAN: For Dr. Mignot also, you mentioned that cataplexy probably is the result of what you called dissociated REM. However, if I recall correctly, the polysomnographic analysis has shown that Xyrem actually decreases the amount of REM sleep and increases delta sleep. Would you like to speculate on what could be the mechanism of action to improve the cataleptic component?

DR. MIGNOT: That is a very, very difficult question. One of the difficult questions, of course, is the mode of action of GHB. I have looked into it myself for quite a while because I was trained as a pharmacologist, and it is not clear. There are two camps. Some people think it acts on GHB receptors, specific receptors; others think that it acts through the GABA-B receptors. We know that it has some strong effect on dopamine transmission. If you inject GHB in

animals the rate of activity of dopaminergic cells shuts down and dopamine can increase in the brain proportionally to the dose. We have done quite a bit of studies that have shown that the

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dopaminergic system is very important to regulate both wakefulness and also cataplexy and the regulation of emotion. I believe it is by changing the balance of the dopaminergic system, that improves cataplexy the following day maybe by increasing dopamine in the brain during the night, but this is highly speculative and a lot more research needs to be done.

The fact that it does not increase REM -- first, it is quite variable because some studies have shown that it does increase REM and this contrasts dramatically with what all hypnotics do. If you take MVN or all the other benzodiazepine-like hypnotics, what they do is actually, rather, reduce slow wave sleep and reduce REM sleep. Xyrem doesn't do that. It actually promotes slow wave sleep and, if anything, would promote REM sleep or doesn't change it. That is still, you know, much more in the right direction of promoting normal sleep, including REM sleep.

The last comment I want to mention is that it is not sufficient -- if you know a lot about narcolepsy, it is not sufficient to just explain narcolepsy as a disorder of REM sleep. Indeed, they have all this transition to REM sleep but they

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also have impaired wakefulness per se. For example, if you do MSLTs they don't always go into REM. They will often just fall asleep into normal sleep. So, it is not only REM sleep that is

disregulated in narcolepsy, it is also wakefulness and by improving slow wave sleep you presumably also can improve the wake aspect of narcolepsy. My answer may be a little complicated but I would be happy to discuss it in more detail.

DR. KAWAS: Dr. Van Belle?

DR. BLACK: Just another comment on that, the Broughton study showed an increase in REM at a lower dose. The first dose of the SXB-20 that I participated in showed at 4.5 g the first night an increase in REM, which was then followed by a dose-related decrease in REM over time, which is very different from REM suppressant agents where there is a robust, or in fact the largest effect that can often be seen on the first night of administration.

So, we don't know exactly why it is that over time the REM with higher doses is reduced, and why with the first dose, and with the lower doses, as has been demonstrated here with Roger Broughton's work, why the REM is increased. There

has been established sort of a competitive reaction between slow wave sleep and REM sleep. It appears that there may be factors that regulate slow wave sleep that also are important in regulating the appearance, or lack thereof, of REM sleep. It may be that gama hydroxybutyrate is sort of normalizing slow wave activity which then results in a more normal control or regulation of the REM or REM-related events.

DR. KAWAS: Can I ask for my clarification, what dose the company is proposing?

DR. REARDAN: Bill, can you take that

question?

DR. HOUGHTON: Yes, the dosage regimen that we are proposing is that patients be started at 4.5 g and then titrated between the range of 3-9 g to clinical efficacy. Although in the strictest mathematical sense the only statistical efficacy in the GHB-2 study was clearly defined at 9 g, that may well represent that the study was too short because in the open-label study that followed, as I showed, the maximum nadir occurred at 8 weeks, and when those patients were followed over the course of 12 months they maintained efficacy across the dose range. Certainly, there is an advantage in

terms of the important side effects to dose titration. In all of the treatment IND protocols and the safety studies the data was generated at between 3-9 g. Now, 80 percent of the patients were maintained between 6 g and 9 g, but there was certainly facility for down-titration from the 4.5 or maintenance there as well.

DR. KAWAS: Thank you. Dr. Van Belle?

DR. VAN BELLE: It seems to me that there is reasonable agreement with respect to efficacy for cataplexy at least between the FDA and the sponsor. So, I would like to get back to the secondary endpoints. I would like to ask a question to the sponsor's statistician, Dr. Trout, as to whether he thinks that multiple comparisons is a problem. Secondly, if multiple comparisons are a problem, how he would adjust.

DR. REARDAN: Do you want to put this in relation to a specific trial or all the trials in general?

DR. VAN BELLE: Well, I bring it up in

connection with the analysis of Dr. Mani where he clearly comes to conclusions that differ from yours with respect to the efficacy of some of these secondary endpoints.

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DR. TROUT: You know, it is hard to answer that question. I think the way I would answer that is as follows: The GHB-2 analysis, the results that we found and also that were expressed earlier were very strong. So, even with the fact that there is some multiplicity, we also have, remember, some other outcome measures which were related to this particular general area in terms of daytime sleep attacks. So, there were at least two measures that suggested improvement with respect to that particular outcome.

The other second study that has been discussed is the Lammers study, and that study is obviously much smaller. It is obviously a weaker study, and there is some issue with regard to whether the appropriate method of analysis was there. So, I think that is a harder one to address.

Now, there are two kinds of multiplicity going on here, which you are well aware of. One is the multiplicity with regard to the multiple dosing levels and that was accounted for in our analyses. The question that was brought up by Dr. Mani with regard to the multiplicity of secondary endpoints, and I am not a betting man but I think there is

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certainly evidence to suggest that daytime sleepiness is being affected possibly. But I don't go to Las Vegas nor Atlantic City.

DR. KAWAS: Actually, while we have Dr.

Trout up, I would ask him with regard to excessive sleepiness on the Epworth Scale in the GHB-2 study, while there certainly was a difference in the two groups, there were also major baseline differences in sleepiness for the responders and the non-responders. In fact, those that appeared to respond had a baseline that was better than the improvement in the other group. There was a significant difference. Are you concerned about these and how these might affect the results?

DR. TROUT: There is always concern about baseline differences, and that was attempted to be accounted for in two mechanisms, one, we looked at change from baseline and we also did a covariate adjustment to try to account for that.

DR. KAWAS: Dr. Katz?

DR. KATZ: I would like to ask Dr. Trout a question also. Dr. Yan mentioned that we didn't believe that the data were normally distributed, and when you transformed the data it didn't really help very much. I don't want to get bogged down in

a hyper-arcane discussion about normally distributed data, but when we did that we got a p value for that comparison -- I guess it was the Epworth, of about 0.01 --

DR. MANI: I am sorry, it wasn't the Epworth. You are talking about the Lammers study where you are talking about the frequency --

DR. KATZ: I thought we were talking about GHB-2.

DR. MANI: Oh, sorry, fine.

DR. KATZ: So, if we are right, it takes the p value which was 0.0001 or something like that

to 0.01, and then when you get to the multiple comparisons issue it makes it less weak. I agree if you take a p value of 0.001 or 0.0001, no matter what you do to it as far as a multiple comparison, it is still going to be significant. But if it is 0.01 it is a little different story. So, I am just wondering, again without getting into excruciating details, what about this question of the data being normally distributed and not necessarily being improved very much by transforming it? Is there common agreement about that or not?

DR. TROUT: My recollection, and it has been sometime since I have seen the results of the

analysis, is that it suggested that we didn't see a particular problem with the normal distribution as, for example, was the case with cataplexy which was clear. I am not sure if Dr. Yan did a nonparametric covariance analysis or not. I haven't seen those analyses. And, I think the point was made earlier that that would be, I think, an appropriate thing to do in order to account for some potential baseline differences. If she did, then whether it is a reflection of a decreased sensitivity of a nonparametric analysis or whether it is a normal distribution -- I can't answer that without seeing the data. Maybe it was just a standard, nonparametric analysis which might help account for the difference.

[Comment away from microphone; inaudible]

DR. TROUT: No, I know that but Dr. Yan did a nonparametric analysis because she was concerned about the normality, and did look at the log transformation and it didn't have any impact on that, which doesn't surprise me at all.

DR. KAWAS: I would like to ask the sponsor, I mean, there clearly was a dose relationship in terms of the adverse events. Were any other factors looked at that may be related to

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the adverse event profile, things like age, even previous psychiatric history, other medications? Whether or not they drank alcohol? Anything?

DR. HOUGHTON: No, we didn't go as far as an alcohol history. Certainly for the major psychiatric, a preexisting history of major psychiatric disease emerged. Major psychiatric disease was actually a protocol exclusionary criterion, but in those that, for instance attempted suicide, post-study it was discovered that they had a previous psychiatric history and in actual fact in one of the patients a previous suicide attempt had been made. There was major depressive disease reported in those, but for those who developed psychosis there was definite recorded preexisting psychiatric history.

In terms of age, we haven't done a breakdown of the database, and in most instances there was not a dose relationship. There were just instances that were mentioned in the presentation. Confusion and sleepwalking suggested a dose relationship. In the GHB-2 protocol which was obviously blinded, there was the association with nausea, vomiting, confusion and enuresis that was definite, but that didn't extend across the whole

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study database. So, the relationship with dose is not well defined.

DR. KAWAS: But how about relationship with anything else? For example, were the patients

who had confusion more likely to be the elder patients? You might be able to tell I am in aging.

DR. HOUGHTON: I can identify well. Do we have a breakdown of confusion by age? A range would be still useful.

[Slide]

Here is a slide that shows that the distribution of age was between 25 and 73 years, with 67 percent over 50 years of age, but the range is still wide. There is the distribution across doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8 events at 7.5, and 13 events at 9 g.

DR. KAWAS: Thank you. Do we have any other questions from the committee? If not, we will move on. Dr. Katz?

DR. KATZ: A quick question, if I heard you correctly, there were 14 events reported as convulsions, but when you went back and looked at that, 13 of them were actually cataplexy. So, presumably cataplexy was a verbatim term. How is it that cataplexy got coded as convulsions?

DR. REARDAN: The COSTART dictionary puts cataplexy in as a convulsion. It is a definition. Convulsion has ten different terminologies, verbatim events, and they all code up to convulsion.

DR. WOLINSKY: Along those lines, how come there were only that few number of convulsions when we were studying cataplexy in the trial? I mean, I don't know that it is easy to explain this in both sides of one's mouth.

DR. HOUGHTON: No, and we are not trying to. If there was a cataplexy event that occurred

of a severity to be seen as unusual for that patient, and the patient volunteered it as an event, then it was recorded as an adverse event. Or, there may have been injury related to the cataplexy events. We do have representation in the database. I can recall absolutely a fractured ankle in the washout study. So, there were traumatic events associated with a major cataplexy event that would have been of sufficient impression on the patient to report as a separate event.

DR. WOLINSKY: But then the event would not have been withdrawal from the primary measure of efficacy even though it was also registered as

an adverse event?

DR. HOUGHTON: I am sorry?

DR. WOLINSKY: Was it still counted as an event in the measure of efficacy if it was also shifted to be counted as an adverse event?

DR. REARDAN: Yes, the patient diaries recorded cataplexy. If they record cataplexy as an event itself, that was part of the efficacy outcome. It wasn't necessarily an adverse event. If they had an adverse event -- fall and break an ankle, cataplexy is coded as part of that adverse event. It is the cause of the adverse event and so it shows up in the database.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I have two questions. One really was just a clarification of this business about the sleepiness. I think we have all agreed that there has to be some adjustment for multiple comparisons on the sleepiness index, and the GHB-2 study, even if you make an adjustment, there are certainly some of the indices about sleepiness

which seem to be significant. But coming back to the Lammers study, have we established whether or not, once we have made an adjustment, we have any significance there or not? Because that is the

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pivotal trial, isn't it, because we need two?

DR. REARDAN: Remember that the Lammers study was a very small trial, 24 patients. Daytime sleepiness was a secondary endpoint in that study, and I forget the p value. Maybe Dr. Yan or Dr. Katz could comment. I don't think any formal study of multiple analysis was done, except maybe by Dr. Yan --

DR. YAN: No.

DR. REARDAN: -- and I think she needs to comment on that.

DR. YAN: For Lammers study there was no prespecified analysis, except the Wilcoxon assigned rank test. It was across the study and we considered it not very appropriate, and for a secondary analysis none of the statistical analyses were specified. The problem with this Lammers study is that if you use different statistical analyses which are considered appropriate, you get a very different result. Some could be less than 0.05 and some ranged to something like 0.2. So, the results are not consistent and we don't have a reliable method to see which one we could consider.

DR. REARDAN: We don't disagree with that. I mean, the problem with Lammers is that it was a

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one-sentence statement about how he was going to analyze it, and it was an inappropriate statistical analysis for a crossover study. So, that creates issues about not having a prospective statistical

plan appropriate for the study. But even in that initial Wilcoxon analysis the daytime sleepiness was statistically significant. It was not corrected for multiple analyses.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I just have another question that I wondered if you could clarify. In a lot of these studies you talk about an intent-to-treat analysis, but when I read it I wasn't clear whether or not that meant the patients that were randomized were actually included always in the analysis or not.

DR. REARDAN: Yes, the intent-to-treat would include every patient who received drug. Is that correct?

DR. TROUT: Yes, every patient who received at least one dose.

DR. SIMPSON: So, how did you then deal with the patients who dropped out?

DR. TROUT: In the GHB-2 analysis we selected an endpoint. So, in order for the patient

to be included in that analysis there had to be at least one post-baseline measure of cataplexy or sleepiness, or whichever outcome you want. So, it was an endpoint analysis that was done in order to accommodate that.

DR. KAWAS: It looks like we are completely behind schedule and we will have a very late lunch, I will warn everyone. The FDA's invited speakers on risk management issues is the next component of this discussion. The first speaker is going to be Dr. Carol Falkowski, of the Hazelden Foundation, in Minnesota, who will be

speaking on the epidemiology of GHB abuse issues.

FDA Invited Speakers on Risk Management Issues

Epidemiology of GHB Abuse Issues

DR. FALKOWSKI: Hello. Good morning, almost afternoon.

[Slide]

This is the title of my talk, GHB Abuse in the United States. I am Director of Research Communications at the Hazelden Foundation. I have been a member of the National Institute on Drug Abuse's Community Epidemiology Work Group since 1986. I am author of a book, called, "Dangerous Drugs: An Easy-to-Use Reference for Parents and

Professionals." What is missing from this overhead is that I served on the Drug Abuse Advisory Committee for the FDA from 1995 through 1999.

[Slide]

In the very short time that I have, I am going to try and just hit the big points about what we know about the abuse of GHB in the United States, starting off with measuring drug abuse. There are a number of things that are thought to bear when we talk about measuring something as complex and multi-dimensional as drug abuse. This includes population surveys. It includes hospital emergency room episodes; medical examiner data; addiction treatment data; law enforcement data, as well as ethnographic studies that look at specific populations of users that are more anthropological and ethnographic in nature.

[Slide]

I also want to make the point that all data systems have limitations, and this is particularly true in the case of new drugs of

abuse. For example, if we are talking about GHB and trying to measure the number of patients who have presented to addiction treatment centers across the country with GHB as their primary drug

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of abuse, it is now the case that it is often grouped in a category of drugs called sedative hypnotics. It is not its own line item. So, in preparation for a meeting like this it is very hard to get an accurate count of the extent to which GHB itself is the presenting drug of abuse.

Similarly, surveys that are conducted -- we have not added GHB to the National Household Survey or the Monitoring the Future Survey, although to the Monitoring the Future Survey that looks at drug use among 8th, 10th and 12th graders ecstasy, another club drug, has been added.

Also, in terms of law enforcement indicators, there is no field test for GHB so it is hard to also get that indication of it as well.

In addition, new methods of abuse are hard to track. I recall, in 1986, when we started at the national level wanting to track crack cocaine, we knew about how to track cocaine but, all of a sudden, we were looking at it by a different route of administration. So, it was a challenge to all of us to start switching our data systems just to measure crack instead of cocaine, to make that distinction.

Existing data systems are slow to respond,

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and there is a system-wide learning curve when a new drug of abuse appears on the scene. That means it is a learning curve in terms of emergency room personnel, treatment providers, law enforcement, as

well as prevention agencies, and that is why we rely on a lot of the scientific literature put out, particularly in emergency medicine, to inform the field about emerging drugs of abuse and how people present with those problems.

[Slide]

My background in this has been as part of the Community Epidemiology Work Group. This is a group of drug abuse researchers from twenty cities in the country that has been convened by the National Institute on Drug Abuse since 1976. This model of drug abuse epidemiology has also been adapted in different parts of the world. There is a similar group in Europe, in Canada, Mexico and Asian cities.

[Slide]

The Community Epidemiology Work Group is an early warning epidemiological surveillance network that detects new drugs of abuse, patterns of use and populations at risk.

[Slide]

It involves researchers looking at the same data from different geographic areas and in this case, as I mentioned, there are people like me in twenty cities in the country who write quantitative reports on drug abuse twice annually, and we are convened by the National Institute on Drug Abuse twice a year.

[Slide]

Having done this and written over twenty reports on drug abuse trends in my city and met with my colleagues, it has given me a sort of broad-based perspective on how emerging drugs are

measured and how we get a handle on them. But everyone looks at medical examiner data. We look at the data from the Drug Abuse Warning Network, which is data from a representative sample of nine federal short-stay hospitals with 24-hour emergency rooms, and that is conducted in 21 cities, as well as some other areas of the country.

We also look at treatment data, law enforcement data and price, purity, trafficking and the sale of drugs, as well as supplemental research data and information from multiple sources.

[Slide]

I want to start my introduction to GHB by

telling you about the abuse of a group of drugs that are called club drugs. That is really the first time in a long time we have had a name like club drugs applied to drugs because they are used in a particular setting. That is why they came to be called club drugs. It is a mixed category of drugs. It includes stimulant drugs as well as depressant drugs that are used in nightclub settings. GHB is also known in these settings as liquid X, gamma, G, easy lay, Georgia Home Boy or great hormones at bedtime. MDMA or 3,4 methylene dioxide methamphetamine is ecstasy, e or x. Ketamine is known as special K. It is a veterinary anesthetic, a dissociative drug similar in effects to PCP. Flunitrazepam, Rohypnol is a long-acting benzodiazepine, which was dubbed the original date rape drug which is a drug not approved for medical use in this country; methamphetamine and LSD.

If there is one point to make about club drugs as a term, one thing that has emerged is the fact that clearly these drugs are not limited to

club settings and I will be talking to that in a moment. It is not just clubs where they are used.

[Slide]

To give you a little slice of the

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progression of GHB and how it came on the CEWG radar screen, it was first mentioned in 1990 through a poison information center from my colleague in Miami. Then, from 1990 to 1994 it appeared in the Miami and the New York city reports. In 1996 it appeared in 6 other cities, and by the year 2000 most cities in this 21-city work group were reporting GHB. It reports 23 deaths in the 20 CEWG cities, and I refer you to a handout that I prepared that sort of gives the chronology of how my colleagues describe the growing abuse of GHB in their cities.

[Slide]

Now, in terms of user typologies, they tend to be young adolescents through adulthood. There is really no age group but when we look at population surveys in this country of who are drug abusers, by and large the biggest bulk of drug abusers are people who are under the age of 35.

The motive for use is multiple. It includes not only intoxication, but also people seeking intoxication effects in the absence of alcohol. I have had people describe it to me as it gives them the effects of alcohol without having to waste that time drinking alcohol. This is by young

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people who haven't developed the taste.

It is also used by weight lifters and body builders for its alleged anabolic effects. It is also marketed in nutritional supplements to promote

better sex, better sleep and some people take it to counter the effects of other club drugs. One of the characteristics of drug abuse in nightclubs that has come up over the past year is the fact that people seem to have the impression that if you take just a little bit of this and a little bit of that nothing can really hurt you in a club setting. So, you might take a little bit of ecstasy to get you going, with a little bit of cocaine to keep you there, and maybe a little bit of heroin to take the edge off. This sort of mixing and matching is also part of the user typology.

The settings it is used in are nightclubs, raves, parties, but also in homes, in health clubs, gyms and other settings. The sources of it come from health food stores, mail order kits, the Internet or at these clubs where it is being used by the capful. Sometimes at these clubs, because ecstasy dehydrates you, people have a lot of water bottles and it is not unusual to have a water bottle that may have GHB mixed in it, and for ten

bucks someone can get a swig of it. This makes it very imprecise dosing, as you can imagine.

[Slide]

In terms of deaths, in terms of the consequences of use -- there is a huge bullet missing from this slide, which I will get to. So, if everybody wants to find their slides and write a bullet in it, I would appreciate it. Deaths -- there have been 71 documented deaths, according to the Drug Enforcement Administration, through November of last year. Again, the problem is that because it is a new drug of abuse people don't

know. You know, you have to know what you are looking for to be able to find something and this has clearly been the case in trying to document GHB deaths. It is a huge issue and I hope we get enlightened on that this afternoon.

Also, there have been adverse medical reactions, not only people who come into emergency rooms, but the countless people, which is quite hard to quantify, who have episodes but never get emergency room treatment for it. But there have been medical reactions, adverse ones.

Dependence -- there has been a reported increase in people presenting to addiction

treatment centers with GHB as their primary substance of abuse, and an increase in the reported addiction to GHB by those who may not make it to treatment programs.

I work at the Hazelden Foundation. We are based in Center City, Minnesota, with campuses in Chicago, New York City and West Palm Beach. There were 5 patients in 1999 who had a history of GHB abuse, and that had grown to 39 in the year 2000 and we are just one treatment center.

Finally, the missing bullet on here is drug rape. One thing we have seen in this country since the early 1990's is the use of drugs, this predatory use of drugs where you administer drugs to people without their knowledge for the purpose of disabling them to commit crime on them. The first drug that came to this sort of notoriety was Rohypnol, but now we are in a situation where GHB is often used in drug-induced rape. In fact, several years ago when President Clinton signed the federal date-rape law, the Samantha Reid and Hilary

Farris Date Rape Act, that was in response to two cases of drug rape that were not related to Rohypnol but to GHB. So, that bullet should be up there, drug rape.

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Also, another bullet would include the trafficking, sale and manufacture, the law enforcement consequences.

[Slide]

Let's look at hospital emergency room episodes of GHB. This looks at them from 1994 through 1999. You can see the increase in hospital emergency department mentions of GHB. Mentions is sort of unusual term for people who aren't familiar with the Drug Abuse Warning Network, and it quite literally means, in a retrospective review of patient records, that they find a mention of GHB. Sometimes it is the sole drug that precipitated the medical emergency and sometimes it is used in combination with other drugs. For every drug abuse episode in the Drug Abuse Warning Network there can be the mention of 4 drugs and alcohol, but when alcohol is used in combination with other drugs; it is not an alcohol tracking system.

[Slide]

So, this is what it looks like through 1999. This looks at it by half year increments. You can see this takes us into the year 2000 and we have the first half of the year 2000.

I want to go back to just my opening

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remarks about club drug abuse. I think in the general population when we think of club drugs, you know, what we hear about, what everybody is talking about, what seems to be in U.S. News and World

Report, in Newsweek and Time Magazine is ecstasy.

[Slide]

This is from exactly one year ago. This is Time Magazine from June 5, 2000. It talks about ecstasy. For many folks, club drugs -- you think ecstasy.

[Slide]

This was, I believe, from Time magazine as well. You see the water bottle there. If you didn't see Time magazine, you may have seen The New York Times Sunday magazine insert. This is from January of this year, talking again about ecstasy. This is from January 2001.

So, since it is in the same category of drug, I think it is relevant to look at how GHB emergency room episodes compare with those of ecstasy.

[Slide]

Ecstasy, or MDMA, is in the pink and GHB is in blue. You can see in the first half of the year 2000 that GHB hospital emergency episodes have

surpassed those of ecstasy.

[Slide]

Efforts to control GHB -- a number of states have done things to try to control GHB abuse in their states. This is sort of a listing of the scheduling of it in various different states. It was added, as you know from the materials the committee received, to the Federal Control Substance Act.

[Slide]

Finally in conclusion, GHB is a significant, growing drug of abuse. We have seen

rapid growth in the adverse medical consequences related to GHB since 1999 and, in fact, hospital emergency mentions of GHB now surpass those of ecstasy or MDMA. We have seen rapid growth in adverse medical reactions despite not only federal scheduling but the scheduling in numerous states. We have multiple user typologies. This is not a substance that is sought after simply by people at parties and raves. These products that contain GHB as well as its precursor drugs, GBL and 1,4-BD, are sought after by people who believe the claims on these nutritional supplements and take them for promoting muscle growth, for sleep; and take them

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for better sex, as well, and as I said, use it in sort of predatory way. Dependence is clearly possible.

So in closing, here we have a drug with an established widespread abuse record. With GHB we needn't talk about abuse potential. With GHB we have abuse reality. We have a decade of GHB abuse in this country; a decade of deaths and hospital emergency room episodes and dependence. We have escalating abuse of GHB in spite of recent efforts to control it and, yes, people acquire this drug and its precursors in many ways. But make no mistake, the effects being sought are the GHB effects. The chemical agent in the body that is producing these effects is GHB, and this undisputable fact is entirely relevant to our discussions today.

I have to take issue with the statement from the sponsor that says Xyrem is not the problem. If Xyrem equals GHB, then I believe it is a problem. This drug, if approved, will exist

outside the confines of this room. Patients will use it outside the confines of clinical trials. In America, in 2001 we have a serious, significant and growing problem with GHB abuse in this country, and

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it just so happens that this coincides with Orphan Medical seeking approval for this drug.

This drug already has avid followers, and there is no reason to assume that another source of GHB would not be sought after by these folks, and I think we need to bear that in mind throughout our discussions. Thank you.

DR. KAWAS: Dr. Falkowski, can I ask you one question? With regards to the emergency department data for GHB, I recognize the difficulties of all of this kind of data but, for example, MDMA is not infrequently the only drug and when they go to the emergency room that is clearly because of the MDMA. Can you give us any kind of quantification or semi-quantification? You mentioned that sometimes GHB is the only drug.

DR. FALKOWSKI: The question was how often is GHB used in combination, and let me find that.

DR. KAWAS: For the emergency room data.

DR. FALKOWSKI: Yes, that is what I am looking for. I have it right here. It is 70 percent of the time. Like many other drugs, GHB episodes involve drugs other than GHB as well.

I would also like to add that I believe these hospital emergency room episodes

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underestimate GHB because drugs that are used in a predatory way, that are administered to people without their knowledge are not DAWN reportable. So, if someone comes to the emergency room and says

I believe somebody gave me something and it is making me sick, that is not a DAWN reportable thing. That is being addressed by the Substance Abuse and Mental Health Services Administration. But what that means is that people who are drugged with any sort of drug are not picked up by this particular reporting system.

DR. KAWAS: And, what are the most common drugs or classes of drugs that go along with GHB when people take them in combination? What are the favorites?

DR. FALKOWSKI: It is probably ecstasy, MDMA, and to a lesser extent ketamine and also alcohol.

DR. SANNERUD: I have some data on the DAWN statistics too. When drugs are used in combination, 50 percent alcohol, 11 percent stimulants, 8 percent marijuana, poly drugs, hallucinogens and sedatives and all these are at least at 3 and 2 percent each.

DR. KAWAS: Dr. Dyer, I believe you are

our next speaker.

DR. KATZ: Claudia, if I could just ask a question, and I don't know who best to direct it, but you said 70 percent of the time the reports are of GHB in association with something else. So, presumably 30 percent of the time it is the sole drug. I have a sort of methadologic question. How reliable would you say that information is, just in general? What is sort of the nature of the information that is recorded and from whom that allows us to conclude that, in fact, GHB is the only drug that was taken? Who reports that, and

how reliable are those reports, just as a general rule? Number one.

Number two, how many of the deaths and very serious adverse events were associated with GHB use alone?

DR. FALKOWSKI: I believe you could address the reliability of DAWN. You are a DAWN reporter. Again, regarding the deaths, you know, the Drug Abuse Warning Network also collects data from medical examiners, but the people in the 20-city work group of mine rely more often on getting data directly from the medical examiners, first because it is more timely and also because it

casts a better net. It captures situations that are not only due to drug-related toxicity but also ones where the use of drugs were considered by the medical examiner to be significant contributing factors to the death. So, that is what I can say about deaths.

Also, I have a table, if you are interested, that I could make available that shows exactly DAWN emergency room data for 1999 and what were the co-ingestants.

DR. KAWAS: Our next speaker is Dr. Jo Ellen Dyer, from the California Poison Control System at UCSF, speaking on adverse medical effects with GHB.

Adverse Medical Effects with GHB

DR. DYER: Thank you and good afternoon.

[Slide]

In 1990 I identified and made the first reports on GHB abuse from over-the-counter sales of GHB. Over the next 11 years I have been following GHB. I have an interest in it and I have been

reporting on the progress, the adverse effects and the trends in use.

[Slide]

This is a description of the California

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Poison Control System data of GHB reports to our center. We logged these reports over 10 years. The first years are when the San Francisco center stood alone so it is a population base of 7 or 8 million. We became a system in '97 so we have 4 years of data for the entire state.

We are a medical toxicology consult service, so we are not a required or mandatory reporting center. So, this reflects just the tip of the iceberg of use and abuse and adverse effects that are out there.

[Slide]

In our experience GHB produces a profound coma. This has been known for over 40 years, starting out in surgical anesthetic studies where it was evaluated as an anesthetic and now through numerous occurrences of coma in users through this widespread public use, where accidental overdoses are occurring because of the narrow and variable therapeutic index for this drug.

[Slide]

Looking at 5 studies, anesthetic studies that cover over 700 patients -- there are many other studies; I just picked a small set of them -- you see the effects of GHB in a controlled

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situation. GHB causes unconsciousness and a profound coma. This is what is intended with an anesthetic. The respiratory effects that are seen are Cheyne-stokes respiration. There were

aspirations. There was a case of unexplained pulmonary edema. In many of these cases the patients are intubated and the airway is attended to. If their airway was left to chance in these situations, it would be compromised. They lose their airway protective reflexes. They have no gag. So, with the high incidence of vomiting, about 30 percent in these studies, combined with the loss of gag, it is not difficult to see how aspiration is going to occur.

There are cardiovascular effects, like bradycardia, and then there are isolated incidences where blood pressure rose up to 30-60 mmHg for unexplained reasons really. There is myoclonus that we see. There is an emergence delirium, confusion. There are also secretions like salivation, vomiting, incontinence and diaphoresis.

[Slide]

If I look at 16 reports that cover 175 cases of adverse events where GHB was in public use, you see these same physiologic responses to

GHB. You have profound coma. They develop a mild respiratory acidosis; bradycardia; myoclonus; confusion; emergence delirium; and then the secretions. This raises doubts for safety of use among a generalized public population.

[Slide]

If we look at a closer group where we did a study in our emergency department, and this is the San Francisco County emergency room that sees over 200 patients a day -- we looked at GHB overdoses that we had over 3 years. This is just a retrospective descriptive study where we were

trying to get a handle on what is going on. We found that of those cases, about 33 percent had no co-ingestion. This was documented by either toxicology or patient report. Those patients came in, a quarter of them, with Glasgow Coma Score of 3. So, they were profoundly comatose and 33 percent of them had coma scores between 4-8. The coma lasted 15 minutes to 6 hours.

Again, a third of the patients had these same symptoms, bradycardia, respiratory acidosis, hypothermia, vomiting. We saw hypotension in about 11 percent. Those cases were primarily cases where alcohol was co-ingested. Then, on emergence these

patients are difficult to manage. They can have an emergence delirium which includes combative, agitated behavior.

[Slide]

Because of that evidence and wanting to focus in closer and get some GHB levels to find out if that is truly what we were looking at, we did a prospective study over 6 months, looking at 15 cases of GHB overdose, and 73 percent of those came in with a Glasgow Coma Score of 3. Our intent was to document the presence of GHB, to detect the co-ingestants and what they were or if there were none, and then to verify that our ability to predict an overdose is truly GHB by the toxidrome that we are using, whether or not that was effective.

So, all of these 15 cases did have GHB that was measurable. They were young, ages 20-39; 73 percent were male. The study inclusion criteria were patients presenting with Glasgow Coma Scores less than 8 and 73 percent of these patients had a

Glasgow Coma Score less than 3.

In 5 of the cases there were no other drugs or alcohol detected. The GCS was 3 in 80 percent of those cases. So, profound coma from accidental overdose; no other obvious cause.

[Slide]

It is clear to us that there is really substantial evidence that GHB causes coma. Coma is life-threatening, and these deaths are occurring from accident or injury and from respiratory compromise. We are seeing that through aspiration; through apnea; through positional asphyxia -- these are profoundly comatose people, they can't even move to open their airway -- and through pulmonary edema.

[Slide]

So, I have reviewed 20 GHB related fatalities where I had autopsy reports. I just sent letters to medical examiners asking for their reports. In these cases, the ages ranged from 15 to 46 years. Three-quarters of them were male; 20 percent of them had no concurrent ingestions. If we look at those that had co-ingestants, the 80 percent. We will see that many of these substances are legal commonly ingested things. Tylenol was one of them; caffeine; alcohol. The levels of alcohol went up to 0.17 percent. The legal limit for driving ranges from 0.08 to 0.1. So, most of these cases were in the lower range, right around the legal limit of driving, saying that they had maybe one or two drinks and none of these would reach an alcohol level that would cause coma.

[Slide]

The societal costs that were seen from GHB abuse, there are many driving under the influence arrests that have occurred with GHB. There were a whole lot that were not recognized until GHB testing became available and now they are being recognized. I don't go out really and collect this data but there are two vehicular manslaughter, I guess they would call it, cases where a person driving under the influence of GHB has hit and killed another individual. One of those was in '96 and one was in 2000.

Another societal cost is the assaults where the victim is under the influence of GHB given to them or slipped to them by the assailant. It is common enough that they have a term for it. It is called being "scooped" by GHB. The assailant then attacks the victim while they are unconscious or amnestic to the effects of the drug, making prosecution and even reporting of these very, very difficult.

These are 4 cases. There are others. But

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in these GHB was clearly documented as the cause. The first was a woman who was drugged and assaulted by her boss as they went out with a group of colleagues after work. She had GHB in her urine. There were 10 victims of some DJs in Los Angeles that were slipping GHB into drinks and then assaulting them. There was a 24-year old that was eventually prosecuted more for trafficking drugs after a woman had reported an assault to them and, in kind of the bargaining, he admitted, yes, he had drugged her twice with GHB and she has no memory of the first event at all. Nothing. The last is two

15-year old females who were unconscious at a party. One was hospitalized and one of these girls died.

[Slide]

We also see addiction as another burden from GHB abuse. We are currently seeing one to two cases a month at our poison center, and this is eight cases that I collected. The age range is young, 22-38, again three-quarters male. The pattern just continues through all these of the demographics of who is using. Of these, 63 percent started taking GHB for body building. They had what they thought was kind of a legitimate use of

this dietary supplement. In this group, 88 percent of them were employed or students. These were functional members of society that have had trouble now because of this drug. These are not people that really had drug-seeking behavior. The onset of symptoms we see within 1-6 hours. It progresses over a couple of days. The duration is 5-15 days.

Now, these are often unrecognized by healthcare professionals when they present for treatment. GHB abuse addiction is not really very well known out there. These are severe neuropsychiatric symptoms with autonomic instability that we see. I have had physicians who have treated many, many cases of severe alcohol withdrawal that have called me up and said, my gosh, I am impressed; I am so impressed by this withdrawal symptom. The patients become agitated, combative, delirious. They are hallucinating. They require sedation, a milligram a minute of IV Ativan has been used over a few hours to gain control. They require four-point leather

restraints and intensive care. One of the patients in this series died while being hospitalized for GHB withdrawal.

[Slide]

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Substantial and compelling evidence from case reports of accidental poisoning and from toxicology supported adverse events really shows us that these effects are due to GHB. It is not some contaminant or something else that is causing these. And, there is an insufficient or no safety margin between the effective level of the therapeutic dose of these drugs that these people are taking and the dose that causes these effects. As you can see from the sponsor's study, the adverse effects that they are reporting are very similar. The confusion, the nausea, the vomiting are very similar to the things that we are seeing.

One physician, Dr. Gallamberti from Italy, who is doing therapeutic use of GHB withdrawal states talks about a 15 percent problematic GHB use among his population. This can be dose escalation. This can be GHB overdoses up to 10 times a year, or GHB dependence.

[Slide]

This slide just looks at the kinetics to illustrate that there is really a very narrow therapeutic index with this drug and there is a lot of variability. The pharmacokinetics of GHB are capacity-limited absorption, capacity-limited

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elimination. The coefficient of variation of some of these parameters is 50 percent. There is a lot of variation and we don't really know what the consequence in different populations and different

people of these really variable kinetics is going to be, or why they are so variable. You are used to using phenytoin. It has capacity-limited elimination. We know that when you are bumping the dose of a patient on phenytoin you have to be really careful because they can exponentially increase their level. Well, the same thing happens with GHB and we don't know where that is yet. There is not enough experience. And, with phenytoin the absorption is pretty good. We know the bioavailability of IV phenytoin and oral phenytoin. Here, I don't think it is so constant. It really changes with food and there is a capacity-limited absorption that is going to vary between patients. So, this is a really difficult drug to control, particularly orally on an outpatient basis.

[Slide]

So, what is the current level of GHB abuse that is out there? We really don't know. If we wanted to project from one survey that was done,

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Dr. Miotto, a UCLA physician that works addiction medicine did a 45-minute structured interview with 42 GHB users. Among that group, 69 percent had admitted that they had lost consciousness, had periods of consciousness laps from minutes to hours. There was variability in the amnesia dependent upon how often people used. Twenty-eight percent admitted having an overdose; 9 percent had been to the emergency department for an overdose.

Now, there is an interesting misconception here where they don't consider the loss of consciousness to be an overdose, and people

overdose and when they are in a profound coma are not taken to the emergency department. So, there are really some problems there, and this gives us an example of the kind of under-reporting that is out there.

If we try and extrapolate from the amount of drug that we are seeing marketed illicitly, this is just one arrest in Marin County, a small county north of San Francisco, where they had 207 L of butanediol. The average street dose varies around 2 g. If you look at that, that is 103,500 doses in one capture at one house, and there are many, many of these. There are lists of different amounts

that have been busted all over.

Then there is the problem that Carol has already talked about, surveying and policing the issues of this type of new drug abuse. There is no systematic method in place for data collection on this.

There is rapid metabolism of the drug. It clears from the blood in within about 6 hours; it clears from the urine within about 12 hours. We can't test these people and find it. When we are trying to get evidence in a drug assault case, it is gone. It is really difficult to detect. And, should we increase our level of detection to the very, very minute nanogram kind of range, then we are going to start running into the biological background so we aren't even going to be able to do that if we increase our ability to detect. There are also very poor assays currently out there. None of the hospitals have an assay for this, and none of the law enforcement has a field kit for it. So, it has to be taken into a lab and specifically

run through a complicated GC mass spec procedure to get a level out, which is expensive.

The current documentation clearly grossly underestimates the amount of use that is out there.

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And, it is very clear that there is a little, if any, safety margin with GHB use in the therapeutic doses that are proposed. GHB is a very potent new drug of abuse. It has been around 10 years. We thought it was going to come and go as a fad, it hasn't and it is not going to. The use is still increasing.

There is a very high acute toxicity in accidental overdose -- coma, bradycardia, myoclonus, vomiting, aspiration -- we are seeing a lot of it, and it has very high abuse and addiction potential. So, I think that we have to be very careful and it is very difficult to try and minimize these potential risks, the risks of having it get out into the drug abusing population but also among patients that we are going to be giving this drug to take at home. At the poison center, every night at bedtime, 9 to 11 o'clock I am called by people that say, oh, I'm sorry, I accidentally took a double dose of my medication. What should I do? In this case, they are all going to go to the emergency room. There is really not a margin of safety with this drug. Thanks.

DR. KAWAS: Thank you, Dr. Dyer. The next presentation is from the sponsor, presentation on

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risk management and abuse liability, Dr. Bob Balster, from the Medical College of Virginia.

DR. REARDAN: Yes, I would like to now introduce Dr. Balster who will present his views

with respect to abuse liability of Xyrem and GHB. Dr. Balster is a previous chair of the FDA Drug Abuse Advisory Committee and a widely published abuse pharmacologist from the Medical College of Virginia. He is editor and chief of a leading addiction journal, Drug and Alcohol Dependence, and a past president of the College on Problems of Drug Abuse.

Sponsor Presentation on Risk Management and Abuse Liability

DR. BALSTER: Thank you very much, Dayton. Good morning or good afternoon, I guess it is now.

[Slide]

Well, as you have just heard, the development of Xyrem as a medication has taken place in a context of a national epidemic of the abuse of its constituent GHB, and also the abuse of a number of GHB-related drugs that I will tell you about.

As Dr. Houghton told you, Orphan is very well aware of this problem and has consulted many

drug abuse experts to try to understand the problem better. My own analysis of this situation is that Xyrem has certainly not contributed to the problem that exists today with the abuse of this class of compounds. I guess where I may disagree a bit is that I am pretty convinced that Xyrem is not going to be a player in this over the long term.

I think in order to understand and make an appropriate public health response to this situation, you need to know a little bit about what some of the causes are of this GHB abuse problem.

[Slide]

So, I hope to make two points in this presentation. The first point is that I believe that the recent abuse of GHB-like substances probably reflects a ready availability more than their inherent pharmacological propensity for abuse.

I think I will make this point by first off reviewing for you the incredible availability of these compounds, and then also review very quickly scientific studies that have been done on the abuse liability of GHB as it is compared to other drugs of abuse you might be familiar with. Secondly, I believe that Xyrem, if approved for

medical use, will not contribute to the public health problem of the abuse of these GHB-like substances in any significant way.

[Slide]

Before we continue, it is very important to know the cast of characters here. I think next to the federal government, the next worst developer of abbreviations is a drug abuse research community, with MDMA, and PCP, and GHB, and BD -- it must be hard to kind of keep track of the players but, of course, the drug we are talking about here is GHB, gamma hydroxybutyrate. But there are a bunch of other drugs that are basically part of this national drug abuse problem.

You have heard a little bit about them, but these precursors, gamma butyrolactone or GBL, 1,4 butanediol or 1,4-BD are precursor compounds that, if obtained, can be easily and readily converted into GHB. They also can be consumed directly because they are metabolized by the body into GHB. So, they themselves are drugs of abuse

like GHB. Then there are others that are also available.

Now, of all these chemicals only GHB is actually a scheduled drug. It is Schedule I under

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the Controlled Substances Act for the abusable versions, GHB; Schedule III for an approved medical product. So, only GHB is scheduled. Now, GBL is what is called listed so its availability is diminished. These others are still freely available without any drug abuse controls.

[Slide]

You have heard a lot about GHB abuse but I am pretty convinced that what we are seeing here is something that has resulted from an amazing situation of the availability of these compounds. To remind you, GHB was available legally and legitimately through health food stores up through 1990 when you could buy it anywhere, and the abuse problem with this drug began during that period of time.

Then through that time and afterwards GHB could be obtained through the Internet. There was an amazing number of sites set up to sell GHB. Then, as GHB became less easy to get because Internet sources dried up, the Internet sources were selling the precursors, etc., etc. I will show you some data a little bit more, but these precursors are not going to disappear any time soon from public availability. Now that the

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availability of GHB has been restricted by the federal scheduling actions and actions by the FDA, people can now purchase the precursors and make their own GHB. Essentially anyone can do that. It

is a very simple thing and the recipes are right there on the web. As I said before, they themselves are widely abused. So, we have a class of chemicals here that are really basically part of what has been referred to as a GHB abuse problem, but it is really an abuse of a class of drugs, and you saw some evidence on that.

[Slide]

At this point I want to review the scientific literature on the laboratory studies of the abuse potential of GHB. You may wonder why I would want to do that, I mean, why would I want to review literature on abuse potential when the reality of GHB abuse is clear to us from epidemiological data that Dr. Falkowski mentioned and clinical data. The reason to do this is to try to understand what the basis for this is, and to know whether or not this wide abuse is due to some features of this incredible availability, or whether the drug has sort of the inherent pharmacological desirability that you would

associate with a really dangerous drug like cocaine or heroin where, no matter how many billions of dollar we throw at the problem, we are getting nowhere with it, or does GHB represent a drug which is less desirable or has less propensity for use.

[Slide]

Just to remind you, there is a well-established science of abuse liability evaluation, and it is used in evaluating new compounds that are under development. It is useful in making decisions about drug abuse control, and data such as these are used widely by the FDA for

making regulatory decisions. All of these data are reviewed in your packages, but just to quickly tell you, first off, GHB is a unique drug. It is not just another depressant drug like barbiturates or even benzodiazepines that have its own receptor and its own characteristics.

In studies which are called drug discrimination studies, which allow you in a way to compare unknown drugs to known drugs of abuse, again, GHB lacks equivalence to these classical depressants like barbiturates or any other classes of drugs to which it has been directly compared.

In self-administration studies -- these

are laboratory studies where you can actually measure what we call the reinforcing effects of the euphorigenic potential of these drugs -- actually in this particular class of studies GHB has very weak reinforcing effects. It is difficult to obtain them in laboratory studies and there have been a number of those. We did one of these ourselves in our laboratory and we essentially found no evidence of GHB self-administration under conditions where we reliably get self-administration of cocaine, heroin, barbiturates, etc., etc.

The case of physical dependence is a little bit more complicated. You heard from Dr. Dyer about the fact that abusers can develop dependence and show withdrawal signs, and there is no question about that. These people are taking maybe 10 or more times the therapeutic dose. We are talking about 70, 80, 100 grams a day, and they take them every 3 hours or so because they have to maintain the blood level. Yes, in those cases you

get dependence, but in patients receiving Xyrem, where they are getting it in lower doses and they are taking it only in the evening, as you have heard from the reports, there have not been

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significant problems of dependence. So, yes, it can occur in abusers but it isn't really an issue in patients. Importantly, animal studies, for example, where you try to show the dependence of GHB and compare it, for example, to barbiturates, it is not easy to develop a model for GHB dependence in animal studies because it has less inherent dependence producing properties than these other drugs.

[Slide]

So, my conclusion when I reviewed the literature on the scientific studies of GHB, when I was asked to do that, I basically thought it looked a lot like what I would say is a Schedule IV drug. Schedule IV drugs, you remember, are benzodiazepines and chloral hydrate and drugs of this type, and that is sort where it fit. It isn't like cocaine. It isn't like heroin. In fact, that analysis of looking at the data has been made by others with very much the same recommendation as mine, that is, it sort of fits pharmacologically with Schedule IV.

For example, the WHO expert committee which met not too long ago to make a recommendation to the UN Commission, the WHO expert committee

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recommended Schedule IV and, in fact, the UN Commission ultimately placed GHB in Schedule IV. Schedule IV, under the Psychotropic Convention is very analogous really to our Schedule IV that you

are familiar with under the Controlled Substances Act.

[Slide]

We are not here to talk about GHB abuse which we know is a significant problem. We are here to talk about Xyrem and what its role may be in the drug abuse problem in the United States. There are two issues we are really worried about here. Number one, we are worried about the possibility that patients legitimately prescribed Xyrem will abuse it in some way, or misuse it or escalate and then, secondly, we are worried about whether or not it might be diverted into sort of illicit channels and become part of a problem in that way.

[Slide]

Turning first to the issue of patients, first off, I think most of you know, and it is important to always know this, that the development of abuse among patients receiving therapeutic doses of abuse drugs is a much smaller problem than some

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people realize. It is actually fairly unlikely to occur in a general sense. Of course, in the trials with Xyrem there weren't problems of abuse; there wasn't evidence that people were escalating their dose or complaining and asking for more, and that sort of thing.

It is important also to recognize that narcolepsy patients are patients that are receiving controlled substances all the time. The stimulant class of drugs, all those drugs that Dr. Mignot spoke about are all scheduled compounds. In fact, many of them are Schedule II where they can't even

get them half the time because the production controls on Schedule II reduce their availability.

Then the issue about their dependence, if you understand, for example, that with benzodiazepines, when you discontinue benzodiazepine administration you will often see a withdrawal syndrome, well, that is because benzodiazepines have this incredibly long duration of action with active metabolites that accumulate so that the body continually maintains levels of benzodiazepines. So, when you quit using them there is a withdrawal syndrome. With GHB, as you saw from Dr. Houghton's presentation, the duration

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of action is just a couple of hours. It would take many, many, many multiple daily uses, way more than the patients are going to get, to maintain the kind of levels of GHB that would be expected to produce dependence. So, yes, in abuse cases where people are just going all day and all night but not with patients.

[Slide]

Turning now to illicit diversion of Xyrem, first off, that hasn't happened yet. So, we are not aware of any diversion of any Xyrem through any of the products. This is, of course, only in clinical development but I think it is important to know. Most importantly, the company has been very much worried about this issue and has developed a distribution system that you are going to hear about, called the Success Program, which I personally believe is going to substantially prevent any opportunities for diversion. Lastly, Xyrem, whether you approve it or not -- it is going to make very little difference in the overall

availability of this whole class of chemicals in the national scene.

[Slide]

To illustrate that, this slide shows you

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the product amounts anticipated, annual production amounts for this class of chemicals I mentioned to you. So, if Xyrem is approved the anticipated first year production amounts of gamma hydroxybutyrate are about 82,000 kg. GBL, gamma butyrolactone, the precursor that can be made into GHB easily and consumed itself, is 83 million kg, a thousand times more. 1,4-BD which is not a controlled substance and has no drug abuse control under it whatsoever right now, is widely available through all sources in large amounts, and is made in the neighborhood of 377 million kg. For those of you who don't do the metric system, that is 400,000 tons of 1,4-BD. And, all of these drugs are basically substituting for one another. So, whether you take Xyrem in or out of that graph, it is not going to make a difference.

[Slide]

In conclusion, I believe that the epidemic of abuse of GHB-like drugs has resulted really primarily from its extraordinary availability. In fact, when GHB was controlled -- it is hard now to get GHB. It is hard even for me to get GHB as a research scientist. So, the problem has now switched to these precursors that are available.

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Secondly, the scientific studies of GHB show that you are not talking here about cocaine or heroin. It is a weak depressant of maybe the benzodiazepine, chloral hydrate type. Thirdly, I

believe that Xyrem abuse is very unlikely among patients for the reasons I said. Lastly, the contribution of Xyrem to the public health problem, which is the matter of concern, is essentially not significant. So, you know, have your way with the drug in terms of efficacy and safety but I don't think you need to be worried that this drug is going to be a major factor in the drug abuse problem with this class of drugs. Thank you.

DR. KAWAS: Yes, a quick question, Dr. Leiderman.

DR. LEIDERMAN: Yes, I would like to ask Dr. Balster two questions. I would like you to comment on the species of animal that you are addressing when you talk about self-administration in drug discrimination studies. Two, I would like you to comment on the data that those models show with other classes of drugs.

DR. BALSTER: All the studies are reviewed on that slide on abuse potential with laboratory animal studies, using fairly well developed

methodologies. The self-administration studies that Dr. Leiderman referred to were studies that were done in monkeys in sort of a standardized method that is done through a program directed by the College on Drug Dependence. Those are the models, and I can show you data if you give me the time to do it. Maybe later, if the committee is interested, I can show you data. But these are models in which basically it is extremely easy to get animals to actually literally self-inject most of the drugs of abuse -- cocaine, amphetamines, opiates of all types, barbiturates, depressants,

benzodiazepines -- benzodiazepines are a little harder but in the model that was used that I showed the negative results from, benzodiazepines were the positive control. So, basically the only area where that model has been not very successful and underestimates abuse potential is with hallucinogenic drugs and marijuana type drugs.

DR. LEIDERMAN: Yes, many of the Schedule I drugs. DR. REARDAN: We just have about another ten minutes. If we can prevail on the committee, we have one last speaker, and that will be Patti Engel, who is going to describe for you the risk management system that the company has developed to help control diversion. Patti?

Risk Management

MS. ENGEL: Good afternoon. My name is Patti Engel, and I am here today to talk to you about the risk management program for Xyrem, which we call the Xyrem Success Program.

[Slide]

This program will ensure the responsible distribution of Xyrem, namely, to meet two goals. First, to ensure that patients who desperately need the medicine can get it. Secondly, to keep this out of the hands of those people who might abuse it.

[Slide]

To develop this program we consulted broadly with a number of people interested in the issues not only germane to patients but also that of drug abuse. As you can see, we spoke with drug diversion investigators, field law enforcement, forensics experts, toxicologists, pharmaceutical distribution experts, drug abuse trend experts.

[Slide]

Through those discussions we followed FDA's proposed risk management guideline, which is risk management through risk confrontation, in

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essence egging the partners and the shareholders to not only identify the issues but also assess the risks, identify the options and select a strategy. The program that I am going to be sharing with you today is certainly a draft program that the company has designed after discussions with these numerous stakeholders.

[Slide]

This slide I show to you really to point out the standard route of distribution of a pharmaceutical product in our country today. This includes not only commonly used medications like products for blood pressure control or products for arthritis, but also products under Schedule II, including such agents as amphetamines. Typically, a product is manufactured and goes to a number of national, regional and local wholesalers, eventually getting to 63,000 retail drugstores around the country. One can only imagine the number of loading docks, transport vehicles and hands that touch a pharmaceutical product in this traditional distribution system.

[Slide]

As we contemplated the distribution of Xyrem and how to do this responsibly to meet the

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prior stated goals, we determined that a closed distribution system would best fit everyone's needs for this product. The product is manufactured at one single manufacturing facility. It is sent to

one single national specialty pharmacy. Eventually it goes by courier to patients with narcolepsy.

[Slide]

The benefits of this program are that not only is the product distributed from a central location, but all the controls and all the records are in one place.

[Slide]

So, how will this work? Because a number of doctors prescribe medicines for narcolepsy, we will focus our promotional effects on those physicians. They include such specialists as neurologists, pulmonologists, psychiatrists, internal medicine physicians and several primary specialties who practice sleep medicine.

[Slide]

Our small sales force will call on these physicians, communicating the clinical benefits of Xyrem in narcolepsy. At those calls, the sales representatives will also review with each physician something that we call the physician

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Success Program. I will go into the details of this program in a more in depth fashion in just a moment. But it is important to know that each physician will sign that they have reviewed this program with the sales representative and understand the program. I should also note that at no time will we embark upon physician sampling.

[Slide]

I promised to come back to the components of the physician Success Program. I know that many of you received copies of this but I would like to highlight some of the main points. First, because

we know individuals all learn differently -- some by hearing, some by reading, other methods -- we have made this a multi-faceted program which includes videos, brochures, pamphlets that describe four main areas.

The first is to highlight to physicians that the distribution process for Xyrem is different, that their patients won't be able to get this at the corner drugstore. The second important issue that this binder points out to physicians is the dosing and administration of Xyrem. The next important issue is that of home storage and secure handling. The fourth is an important module that

we call "doctor be wary" which is an educational module that educates doctors about the ways that drugs are commonly diverted in this country so they can be aware of patients who are attempting to illegitimately get a prescription from them for this product. Each of the kits will also contain a number of unique prescribing forms for Xyrem which will be necessary in order for the prescription to be filled. This is, in essence, a special prescription form. As well, contact information will be provided should the doctor have any questions at all about the program.

[Slide]

Once the physician decides to prescribe Xyrem the physician faxes this special prescription to the specialty pharmacy. Now, I am going to come back to how this prescription is verified. So, I will ask you to hold on that point for just one moment. But, based on that prescription and based on the patient's geographic location, the pharmacy assigns that patient to a dedicated pharmacy team.

So, each time that the patient deals with the system they are talking with the same pharmacist and the same reimbursement specialist.

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I mentioned that as the prescription comes to the specialty pharmacy there will be a number of checks to determine if the physician is, in fact, eligible to prescribe Xyrem. We will be utilizing DEA's NTIS or National Technical Information Services database to ensure that each physician has an active valid medical license, and also to ensure that that physician has current prescribing privileges which allow him or her to prescribe Schedule III medications in this country. As a backup check, the specialty pharmacy will also be checking with the appropriate state medical board to determine that there are no pending actions on the behalf of the state for that given physician.

[Slide]

As a secondary step, the specialty pharmacy will also do a check on the patient in essence. What they will do is when that prescription comes in they will call the prescribing physician's office to determine that, in fact, that patient is real and a prescription has, in fact, been written for that patient.

[Slide]

Once insurance reimbursement is obtained, the specialty pharmacy contacts the patient, first,

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to determine the patient or the patient designee's location and availability for shipment, and also to describe to them the contents of the shipment. I will come back to the details of this in just a

moment, but it is important that you know that each patient, when they get their first prescription of Xyrem will receive a multi-faceted educational program called the Xyrem patient Success Program, and I will come back to the details of that in just a moment.

In that same shipment they will also receive their Xyrem, and that will look something like this, with child resistant closure not only on the primary container but also on the dosing cups which are provided by the company.

[Slide]

The shipment that goes to the patient is sent by a special system that has a special, unique tracking system called the Rapid Trac System. this system will allow detailed real-time tracking of that package which is delivered only by the authorized signature. If the patient or their designee is not available for receipt of the package at the time agreed upon with the specialty pharmacy, the package will be returned to the

specialty pharmacy after one delivery reattempt. So, a package will not sit on a delivery truck or in a hub for weeks at a time or anything like that. If the package is lost the system will allow an investigation to begin regarding the shipment's whereabouts at that point of loss.

[Slide]

I spoke a moment ago about the patient Success Program. Again, this is a multi-faceted program which includes video, brochures and pamphlets which deal with a number of important issues for patients. First addressed, of course,

is the distribution process since it is so important that the patients understand that the only way they will get Xyrem is through the special pharmacy and not at their corner drugstore.

There is information about Xyrem's dosing and administration because we feel that that is an important message to be delivered in an understandable and a very consistent manner.

There is information on home storage and secure handling, and we also are very clear with patients about the criminal and civil penalties that the public law assigns to any illicit use of Xyrem. So, if I were, as a valid narcolepsy

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patient, to take my Xyrem prescription and use it to conduct a rape or in an assault situation, or if I were to sell it to someone for illicit use I would be penalized, I would be subject to C-I penalties. The patient Success Program also includes contact information for the specialty pharmacy should the patient have any questions at all, and also reimbursement information.

[Slide]

After the Rapid Trac System shows that the package has been received by the patient, the specialty pharmacist will call the patient within 24 hours not only to confirm receipt of that package but also to again reiterate certain important points with the patient. Those include the penalties for illicit use of Xyrem; Xyrem's dosing and administration; home storage and secure handling. The pharmacist will also take the opportunity to discuss with the patient the child-resistant features on the primary container as well as the child-resistant features on the

dosing cups that are provided.

[Slide]

The central data repository designed for Xyrem really allows for identification of a number

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of unusual types of behavior, including any duplicate prescriptions, any attempts of over-prescribing, or any attempts at over-use by patients. The benefit here is that that information is available prior to filling the prescription so appropriate pharmacist intervention can occur.

[Slide]

As you can see, the Xyrem Success Program is a comprehensive program which is designed to responsibly distribute this important medication in order that patients who need it have it available, and it is inaccessible for those who might abuse it. Thank you.

DR. REARDAN: Dr. Kawas, that completes our presentation and we will turn this back over to you.

DR. KAWAS: Thank you very much. I want to thank all of you for all of your nice presentations but, rest assured, you will have more questions in the afternoon. We are running quite late so we are going to cut lunch a little short and we will plan on reconvening at 1:30, at which time the public hearing component of this meeting will happen.

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[Whereupon, at 12:50 p.m., the proceedings were recessed for lunch, to resume at 1:30 p.m.]

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AFTERNOON PROCEEDINGS

DR. KAWAS: We will reconvene the meeting of the Peripheral and Central Nervous System Advisory Committee discussing Xyrem. We are now in the open public hearing portion of this meeting, and we have quite a few people that we will be hearing from and additional people who want to add to the list. I would like to ask all of the speakers to please do their best -- not their best, you must stay to five minutes. You will have a one-minute warning sign with your timer. If you go over, please don't take it personally but you might hear my voice ending your part for the meeting. This is in order to allow us to hear from everybody who wants to speak, as well as to get onto the deliberations of this committee. The first speaker in the public forum is Sharon Fitzgerald of Littleton, Colorado.

Open Public Hearing

MS. FITZGERALD: Good afternoon. I am Sharon Fitzgerald from Littleton, Colorado, and I am a narcoleptic. I am a volunteer member for the Orphan Medical Patient Council and the Narcolepsy Network is paying for my travel and my hotel to allow me the privilege of speaking with you today.

Five minutes isn't long enough. I have provided a longer version for you to read. Please, please read it. It explains my experiences with the five major symptoms of narcolepsy and how Xyrem gave back my American dream, the ability to pursue happiness without stumbling on the way when it gets tough, and without literally falling on my face when the goal of happiness is reached.

I have had daytime sleepiness since 1969. It threatened my ability to be a good mother and

protect my children, and it trapped me in a series of entry level jobs. Not knowing it had a name, I tried to hide my problem from employers and I hid in restrooms for many years for 15-minute naps at unpredictable times lots of the time.

My symptoms dramatically increased and worsened in 1977 when I was in law school. I was raising school age kids on my own, being widowed at the age of 32. In daytime, against my will, I took naps in my classes, going instantly from consciousness to dream state sleep, the switch being so quick that I actually wrote words from my dreams in my class notes about things like my mother and helicopters, and wondered where they came from when I read them. These were usually

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followed by a mark where I dropped my pen as I stopped writing, and that would startle me into wakefulness and I would stay awake for a while and take more notes.

Going to sleep nearly every night, my mind created vivid illusions of my very worst fears, often a murderous rapist breaking into my house from behind wherever I was sitting or lying. My knowledge of where I was, was accurate. I could not scream. I was paralyzed and I couldn't turn around to defend myself. These are called, as you know, hypnagogic hallucinations. I didn't know that at the time.

At the same time, the symptoms of nighttime wakefulness became more severe. I experienced long hours of anxiously lying awake, punctuated by times of intense dreaming so real and so vivid that in the daytime I couldn't remember

whether events I remembered were real or dreamed. You may understand that I feared for my sanity, and this is when I sought medical help.

I was my doctor's first experience with narcolepsy. It took a very long time for him to find a diagnosis. When he did, it was because of my mild cataplexy and he found the diagnosis an

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announced that was the good news because the bad news was there was no treatment. I self-medicated for years with Sudafed and coffee.

With determination -- if you knew me you would know about it -- and special accommodations from the university I actually finally managed to graduate from law school, but I turned down the dream job that was offered, clerking for a district court judge, because I feared I would fall asleep in front of the courtroom. He told me our first case would be about two nuns who had been brutally murdered and I feared I might experience cataplexy.

By this time my cataplexy had increased to the point that all my facial muscles would relax and my speech would become momentarily slurred. It passed so quickly that I couldn't hide it. I was a sole practitioner. I couldn't bill enough hours to earn a living. I took Ritalin; I took antidepressants unsuccessfully. I found a job with the State of Colorado. It didn't require my legal expertise but I got lucky, I found out about the trials. I had rebound cataplexy, like what they showed you in the pictures, and it was horrendous for several weeks, waiting to be on Xyrem and my secret was brought out at work. But they didn't

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fire me because I told them I was going on Xyrem.

Its effects were immediate and dramatic. I have experienced no side effects. I get good restful sleep. I awaken refreshed. I stay reliably awake at work with fewer stimulants and I don't fall down. My supervisors noticed my increased wakefulness and rewarded it with committee chairmanships and memberships and, in 1999, a promotion. In 2000, January 1, I became an administrative law judge for the Division of Workers Compensation in the Colorado Department of Labor and Employment. It is responsible; it is emotional. I can do it. My colleagues know I have narcolepsy and they know that with Xyrem it doesn't interfere with my job performance. For years I was unable to safely carry my children or grandchildren. I carried my newborn to his first examination and that is just the beginning of my story.

DR. KAWAS: Thank you, Ms. Fitzgerald. Next is Richard Gelula, the executive director of the National Sleep Foundation.

MR. GELULA: Thank you. The National Sleep Foundation is an eleven-year old organization that was developed by the American Academy of Sleep

Medicine to educate the public about sleep and sleep disorders, and our leadership has always been drawn from the top tier of sleep experts, sleep scientists and sleep physicians. We are independent. We raise our money in a variety of ways including government grants, corporate grants, and many memberships, individual contributions that have played a major part, particularly from people and families affected by sleep disorders. Our funding from Orphan Medical for the last two years

has been a total of 160,000 out of a two-year total of about 5 million. Our budget is about 2.5 million a year. And, their support has gone to broad activities -- sponsorship for National Sleep Awareness Week where they join in with other sponsors, and there is no name or brand specific recognition or benefit for them. So, I wanted to point that out.

The Foundation is qualified to address this and our interest is due to the fact that we have invested about a million dollars in narcolepsy research, including center grants for the genetic research done at Stanford. We presently have one of our postgraduate fellowships at UCLA studying the neurophysiology of cataplexy. We also have

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established the National Narcolepsy Registry which has registered to serum DNA registry with about 700 patients and family members registered. That is managed at Montefiore Hospital in the Bronx, and it has been a resource for seven scientific investigations.

To summarize the position of the National Sleep Foundation on sodium oxybate, the National Sleep Foundation calls upon this panel to fully consider the safety and efficacy of sodium oxybate for the treatment of narcolepsy and cataplexy, and to do so in a comprehensive context that fully recognizes the extreme psychological, emotional, economic, social and health toll that this affliction exacts from people who suffer from it.

NSF does not presume to second-guess the evidence that has been submitted about the safety and efficacy of this drug, but it goes on record to

say that such considerations should only pertain to affected patients and not other societal considerations. It is safe and effective for people with narcolepsy, like the speaker before me. Sodium oxybate should be made readily available to them. Any concern for illicit use should be addressed strongly through other channels, such as

law enforcement and professional licensing. The fact that narcolepsy is an orphan disease, for which only one medication is currently indicated, would be weighed as a factor in favor of approval of sodium oxybate because it is likely that availability of an approved drug will foster faster diagnosis and more appropriate treatment, and will also -- and we think this is very important -- stabilize patients who usually first experience the dreadful effects of narcolepsy and cataplexy during their developmental years, before the completion of their educations and initiations of a career.

I would like to summarize a few key background points. Narcolepsy and all of its primary characteristics, including cataplexy, are truly life-altering afflictions, a term that best connotes the life-diminishing and debilitating aspects of this disabling disease. Untreated, narcolepsy not only causes vivid nightmares and undermines the safe and secure feeling that most people get when they go to sleep, but it makes daily existence, both objectively and subjectively, frightening and strange, even alienating to the self and others. It makes the well-controlled process that routinely governs the existence for

almost all other humans, the alternating cycle of

sleep and alertness, into something entirely different, an uncontrollable process where the maintenance of conscious attention becomes random and cannot be sustained or relied upon. Both the phenomenon of overwhelming sleep attacks and the muscular weakness and collapse that occur with cataplectic attacks undermine the sense of predictability and confidence required to fully develop and function in our contemporary world.

But a true understanding of narcolepsy goes beyond physiology. The cumulative effects of the distinctive daytime and nighttime characteristics of this disease are truly traumatic. They not only disrupt; they undermine and frighten and change the core experience of the individual, exacting a toll that ranges from difficulty coping and functioning to total disability.

I think some key characteristics that should be taken into consideration are that narcolepsy is not well understood or accepted. People who suffer from this suffer alone. They don't have generally the benefit of support groups, even though there is a fine support organization

out there, but the people are just spread out. There isn't enough concentration. Most people with narcolepsy do not have a relative with the disease such that it is even strange to them. People suffer a double blow because it is thought their sleepiness is volitional and a sign of laziness.

Thus, I think it should come as no surprise that people with narcolepsy suffer from a high rate of depression. It has been estimated from 30-70 percent in various studies. The good

news is that in one study health quality of life was improved through effective administration and medical treatment, and I think that would pertain as well to sodium oxybate.

In sum, the National Sleep Foundation believes that narcolepsy exacts an unusual and cruel toll. We really call upon this panel to continue to do the professional job that brought you here today and fully consider the personal, psychological, emotional and human aspects of this disease and the great need for an effective medication. Thank you.

DR. KAWAS: Thank you, Mr. Gelula. The next speaker is Ms. Abbey Meyers, who is president of the National Organization for Rare Disorders,

Inc.

MS. MEYERS: The National Organization for Rare Disorders, which is known as NORD, came together initially because voluntary agencies for many rare diseases worked together to pass the Orphan Drug Act. So, we are the orphan drug folks who work to monitor the development of these drugs.

I have several conflicts of interest with this drug because for 20 years I begged practically every company I ever met to pick up this drug and to adopt it. It is a 20-year saga. And, I wrote something for you that you will be able to read about the history of development of the drug.

Also, about a year ago I bought some stock in this company. If I wanted to make money I would have put it in Merck, but the idea with the drugs that they are developing is I feel I have to make my own personal investment in the survival of the

company.

For this drug FDA, rightfully, has asked for a risk management program, and there are several really good models to look at, most notably, I would like you to remember when you are discussing the risk management what happened with Clozaril because when Clozaril first got on the

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market with the drug for schizophrenia, they had a very stringent distribution program, and they were sued by 30 states, attorneys general, because the laws in those states said that you could not restrict the distribution. In the settlement of that case, the federal court assigned us, NORD, with the task of distributing the drug to the people in this class action settlement.

So, I am very sensitive to what happens. FDA approved Clozaril's distribution program but then the law said that they couldn't do it. So, people really want the freedom to be able to get the drug when they want it, when their doctor prescribes it.

The other program you should look at is thalidomide because it is an extraordinarily important drug, again very orphan. Nobody wanted to go near it because of the liability problem. But they have a wonderful distribution program and I think it should be a good model for the field when there are drugs with specific dangers involved.

I also want to give you several cautions. Don't make the distribution too restrictive. For example, don't allow just certain specialists to

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prescribe it because people with narcolepsy have a

great deal of travel problems. Many of them don't have driver's licenses in many states. They may hold on to their driver's license but actually if it was ever reported to the state that they had narcolepsy they would lose it. It is just like epilepsy. So, you have to be sensitive to that.

There are many current problems with Ritalin and Dexedrine and the amphetamines that they are using because the government limits the amount of manufacture every year. So, at the end of the year they run out of drug and there are times when they just aren't able to fill their prescriptions and they can't order it by mail order because it is a controlled substance. So, these people have suffered so tremendously because of these distribution problems. With those drugs, pharmacies don't stock a sufficient amount and they will only dispense one month at a time.

Don't require a distribution program that is going to cause legal problems. So, ask yourself that, whether the program that has been designed by Orphan Medical could be loosened up a bit.

The other thing goes back to what you were talking about this morning, labeling. You know,

does this drug help with daytime sleepiness, etc.? I want to caution you that if you label this drug just for cataplexy with no effect on daytime sleepiness, there are a lot of insurance companies that are not going to reimburse for it. So, labeling on a drug is extraordinarily important to patients because of the managed care insurance system. So, try to be as liberal as you can on that, thinking about whether insurance companies are going to say no, except to just people with a

particular type of narcolepsy.

Also, recognize that it is a unique disorder that is just as crippling as epilepsy, and that these people are already paying a very heavy price because of the problems they have with their current drugs.

Illegal use has to be handled, which I know that you are going to do, but you must pay attention to the valid use of this drug. Thank you.

DR. KAWAS: Thank you, Ms. Meyers. You are the first one who hasn't used all of your time and that is greatly appreciated. The next one is Robert L. Cloud, from the Narcolepsy Network.

MR. CLOUD: Good afternoon, and I wish to

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thank the committee for the opportunity to address you on this issue. My name is Bob Cloud, and I would like to briefly talk to you, first about my own long, personal use of Xyrem, and I will call it Xyrem not GHB or sodium oxybate and, secondly, my very serious concerns as director of Narcolepsy Network, which is a national non-profit, primarily patient organization. In that capacity we have received funds, a minor amount of funds, perhaps ten percent of our revenues, from Orphan Medical over the last several years.

First, my personal experience with Xyrem as a narcolepsy patient with cataplexy. I am 57 years old, married, have two adult children, and I am an attorney in private practice, primarily family, probate and criminal law which sometimes can be intense and have a few emotions attached to it.

I believe I am the first American to have used Xyrem for narcolepsy, and I am probably the longest continuing user of Xyrem which now approaches 19 years every night without fail. My narcolepsy/cataplexy symptoms began in the mid-30's and by age 39 included severe and recurring cataplexy together with excessive daytime

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sleepiness and sudden sleep attacks. My cataplexy caused numerous daily episodes of complete body collapse, such that I couldn't leave my office or home without risk of harm to myself or others. Feeling any emotion, humor, anger or mere enthusiasm, would result in sudden immediate collapse. I guess we are all ignorant of what diseases feel like that we don't have them, but my best description of the sudden collapse of cataplexy would be to imagine a puppet on strings and suddenly the strings, which are your muscle tone, are immediately let go and so you fall to the ground immediately, and your head comes down last and whips against whatever -- sidewalk or table corner or escalator or whatever might be there. I have been rescued by police and emergency squads and life guards and well-meaning strangers and friends.

Obviously no injury for me has been fatal because I am here, but unfortunately I do know others whose fall has occurred at the top of the stairs and they fell down backwards and killed themselves, and there are others that I don't know about.

In 1982 my treating physician sent me to

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Sunnybrook Medical Center in Toronto, Canada to

begin prescriptive use of Xyrem under the research being conducted by Dr. Mortimer Mamelak. After three weeks I returned home and continued using Xyrem, always prescribed by my local physician under his own individual investigational new drug application. My severe cataplexy symptoms disappeared almost overnight. I was immediately able to return to my full-time law practice and I have continued to this day to use Xyrem under that individual application and subsequently in the clinical trials under the Orphan Medical application. During these 19 years, I have never changed the dose. I have never experienced tolerance. I have never noted side effects. Simply stated, the drug is as safe and effective as it was on day one. It is hard to imagine a pharmaceutical product having such a quick, complete, safe and enduring benefit.

As director of Narcolepsy Network, I have said on a number of occasions that I think the greatest tragedy in the treatment of people with narcolepsy is that Xyrem or GHB has not been available so that other patients could benefit from it as I have. Hopefully, this committee will

remedy that.

We are sensitive to the reports of injuries and deaths and other victimizations from the abuse of GHB and, as an organization, we work with law enforcement and community drug agencies to partake in their activities to limit that and correct that. I think it is obvious that Orphan Medical is going above and beyond the call of duty to also contribute to restricting the unlawful use of GHB.

In closing, I submit that our concern for patients with narcolepsy should receive your highest considerations so that people can rediscover their economic and particularly their family lives and avoid disability. Thank you.

DR. KAWAS: Thank you, Mr. Cloud. The next speaker is Cindy Pekarick from Pennsylvania.

MS. PEKARICK: Hi. My name is Cindy Pekarick, and I am here today to tell you how GHB killed my daughter. In October of 1998, my daughter Nicole, a college student and gym enthusiast met a new boyfriend who introduced her to a product called Renewtrient. In November she researched the product over the Internet and received only positive information. She could take

it before bedtime and wake up in only four hours feeling refreshed, well-rested, and all her muscles would be completely recovered and ready for another workout.

In December I found out she was taking this supplement. I didn't believe the promises made by the advertisers. Arguments ensued and she promised she wouldn't drink it anymore. She was away at school from mid-January until April.

In April she returned home. She was behind in all her bills. She was black and blue on her arms and legs. She stopped attending classes, and she kept losing things. In May I discovered she had essentially dropped out of school.

In June I could see mild changes in her behavior. She began taking power naps, as she called them. She would sleep three hours in the middle of the day and get up at four o'clock and go

to work. She continued losing things and having difficulty paying her bills. I searched her room and car but found no evidence of substance abuse.

By July, my younger daughter, Noelle, informed me that Nicole was having problems. She said, "mom, she isn't taking anything bad or illegal. She takes a muscle supplement that

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doesn't agree with her. Sometimes she has bad reactions and she doesn't even know it. She embarrasses herself and me when she acts weird and then goes to sleep. When she awakes she never remembers anything that she did. She started taking it once in a while so she could go to sleep right away after work when she got home. Then she started using it more often. It disgusts me to see her out of control."

It was at this time I discovered Nicole had been taking GHB since November. I then began my own search over the Internet for more accurate information. In August, Nicole was found having a seizure in a public bathroom. She had urinated and defecated on herself while pulling at her clothes and hair and flailing her arms. She was rushed to the hospital where we arrived to find her unconscious, intubated, with her arms, legs and waist strapped to the bed. They claimed her seizure was violent. She barely had a pulse when they found her.

It was at this time I knew my daughter was addicted to whatever she was taking. There is absolutely no other reason why a young, bright, healthy woman would take a supplement that was

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harmful. I begged the doctors to transfer her to a

treatment center for chemical dependency, but they said they wouldn't do it without the patient's permission. She was clueless as to why she was hospitalized and she had no recall of anything that happened to her. She was discharged.

In September, Nicole, sweating profusely, with a red face and shaking hands while crying said, "mom, I have to talk to you. I'm really scared. I have a problem. I can't stop drinking it." I stood up, wrapped my arms around her and hugged her as hard as I could. I told her that she was on her way to getting better, that acknowledging that "g" had a hold on her was a step in healing.

On Monday morning, on her way to the treatment center, Nicole refused to go in. She claimed that "g" wasn't addictive; that she did the research and she was just having reactions to it. She said she was now in control of her life and future. She stayed in counseling and, by the end of September, Nicole had applied, transferred, and was accepted at the university. She was excited. Things seemed okay on the surface but she was hiding tremors, hallucinations and insomnia. She

went days without sleeping but never told me.

On October 3, 1999 at 2:00 p.m. she said she needed to take a nap before she went to work since she hadn't slept the night before. She set the alarm for 4:00 p.m. but she never heard it. She was in her final sleep. My firstborn child was found in bed, blue, at 6:00 p.m. We found a bottle of GHB in the trunk of her car. The autopsy revealed she had GHB and GBL in her system at the time of her death. No other chemicals were found.

Nicole was an honor student, captain of two varsity teams and graduated third in her class. For her undergraduate studies she majored in biology, with a plan to major in engineering for her master's degree. Her ultimate goal was to become a biomedical engineer. She wanted to be able to design body parts to help extend people's lives. She understood that to function well, one had to be healthy. She was a loving, sensitive, caring and intelligent woman. Her only fault was that she was naive. Thank you.

DR. KAWAS: Thank you, Mrs. Pekarick. The next speaker is Eric Strain. Doctor Strain is from the College on Problems of Drug Dependence.

DR. STRAIN: Thank you. I would like to

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thank the FDA and the members of the Peripheral and Central Nervous System Drug Advisory Committee for providing me the opportunity to speak. My name is Eric Strain. I am a professor in the Department of Psychiatry at Johns Hopkins University School of Medicine. I am a board-certified psychiatrist with qualifications in addiction psychiatry, and I am here today representing the College on Problems of Drug Dependence, CPDD.

The College is the leading organization of drug abuse scientists in the United States. I am also the former chairman of the FDA's Drug Abuse Advisory Committee. I have sponsored my own travel to today's meeting, and I have no relationship with Orphan or other pharmaceutical companies that make narcolepsy products.

There are two point that I would like to make during these brief comments. The first is

that the College on Problems of Drug Dependence would like to emphasize the importance of science-based assessments of new medications, especially as they relate to issues such as abuse liability evaluation and safety of abused products. The College wishes to stress the long history that has led to the establishment of reliable and valid

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methods for determining abuse potential. This work includes both preclinical as well as clinical studies. Several academic medical centers contain rich experience in this area of research. Methods have been well tested, and outcomes from previous studies have helped inform and guide agencies such as the FDA in making determinations regarding abuse potential, therapeutic efficacy, and safety of new medications.

CPDD has played a key role in such matters, as its members are the primary group that have conducted such studies. The College wishes to strongly and forcefully advocate that decisions made by the FDA grow out of and be based upon well-conducted research, and whenever possible decisions should be derived from well-controlled studies and data driven. In order to achieve such goals, advice on substance abuse related matters should be solicited from experts in the field.

The second point I would like to make has to do with the Drug Abuse Advisory Committee. As the former, and the last chairman of this advisory committee of the FDA, I believe it is important for me to comment upon its termination. The Drug Abuse Advisory Committee has been dissolved by the FDA,

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and in the process the FDA has lost an important

resource that can inform decisions regarding substance abuse. To my knowledge, today's meeting is the first FDA advisory committee meeting since this termination where issues of drug abuse are an important element in your discussions.

I am pleased to see that there are several drug abuse experts represented here today, however, I am concerned that the numbers do not allow the breadth of expertise that would have been found on the DAAC. Such breadth is essential to fully consider all of the issues involved in advising the FDA on the abuse potential of new medications, the extent of the public health consequences of such abuse, additional data that the FDA should require companies provide, and recommendations regarding post-marketing surveillance.

The College is particularly concerned that comparable experience and knowledge brought to the Drug Abuse Advisory Committee by experts in the drug abuse field is no longer readily available to the FDA. In my experience as chairman of the committee, I was able to witness firsthand on repeated occasions the value of having a group of scientists and clinicians who could provide

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informed knowledge and experience to the FDA on matters such as those that appear to be on today's agenda.

The loss of the DACC to the FDA is significant and substantial, and adequate representation of drug abuse issues on other advisory committees needs to be clearly demonstrated by the FDA. I speak on behalf of the College in expressing the College's continued concern regarding the dissolving of this advisory

committee. Given the tragic consequences of drug abuse to our society, as exemplified by the previous speaker, its prevalence and the growing body of medications for the treatment of substance abuse disorders, it is particularly concerning that the FDA has decided to terminate this particular advisory committee.

Again, I wish to thank the FDA and this advisory committee for allowing me to make these comments today. The hope of the College is that these companies will spur tangible demonstration of FDA's commitment to having adequate outside input by experts in the drug abuse field in the advisory committee process either through the renewal of the Drug Abuse Advisory Committee or through adequate

and substantial representation by drug abuse experts on other advisory committees where issues of drug abuse may be of substantial importance. Thank you.

DR. KAWAS: Thank you, Dr. Strain. The next speaker is Deborah Zvorsec. Dr. Zvorsec is from Hennepin County Medical Center in Minnesota.

DR. ZVORSEC: Thank you very much. My research is in the area of gamma hydroxybutyrate abuse toxicity, addition and withdrawal. Dr. Steve Smith and I, with others, published a case series in Morbidity and Mortality Weekly Report in February of '99 that described adverse events due to ingestion of dietary supplements containing GBL, GHB precursor. I was the lead author of a case series of 1,4 butanediol toxicity that was published in The New England Journal of Medicine in January 2001. These toxicity episodes included two

deaths that occurred with no co-intoxicants and no evidence of aspiration or asphyxiation or adulterants.

I will focus today on GHB addiction. In the course of our work, Dr. Smith's and my name were listed on the project GHB help site. We received calls from over 40 addicted patients from

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25 states, and have treated an additional 5 cases of inpatient withdrawal at HCMC in Minneapolis.

The vast majority of these addicted people began using GHB to treat insomnia, anxiety, depression, chemical dependence or for body-building purposes, as recommended by marketers, websites and fringe pro-GHB physicians. Many, indeed, began with GHB, continued with GHB and never used any of the dietary supplement analogs. Our patients began with small doses, often only at night, and discovered that it made them feel good; increased dosing frequency and, as tolerance developed, needed more GHB in order to feel good. Within months, they were taking GHB every one to three hours around the clock to avoid withdrawal symptoms. By the time they realized that they might be physically dependent, attempts to abstain resulted in severe anxiety, insomnia, panic attacks and hallucinations.

Their addiction destroyed their lives. They lost their spouses. They lost access to their children, their jobs. They acquired tremendous debt to support their habit. They became comatose while driving and crashed their cars, frequently on multiple occasions. They called us in absolute

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desperation. Their detox was frequently similar to

the worst cases of delirium tremens, requiring large and often massive doses of sedatives, often with intubation.

Almost all patients suffered weeks or months of profound depression and anxiety after detox, and some also experienced muscle twitching and tremors. Of the over 40 patients we have worked with, only a scant handful have remained GHB-free, frequently despite CD treatment. Many have detox'd numerous times but continue to relapse, sometimes within hours of discharge from treatment. Unfortunately, many never lost faith in GHB and continued to be convinced that they could get back on it and use it responsibly. They continue to argue its health benefits.

One of our patients was a 50-year old businessman with his own business who began using GHB, not an analog, five years ago, initially for body-building purposes. Within months he had increased his dosing to around the clock. His life was entirely controlled by the need to have GHB with him at all times. He tried numerous times to quit. His wife was unaware of his addiction. She described witnessing frequent frightening hypnotic

states, punctuated with clonic movements. She believed that his frequent states of apparent somnambulism were due to a sleep disorder but despaired when a sleep specialist could not cure him. This woman is a very bright professional who was totally unaware of GHB, as is the case with many family members. It was only on the morning of his admission that she learned the truth. After six days of detox he was through the worse and appeared to be on the road to recovery.

Psychiatrists treated him with sleeping meds and antidepressants, but within three days he was using GHB again to control anxiety attacks and depression.

GHB is perhaps the most addictive drug ever abused. Experienced drug users describe a euphoria that surpasses that of any other drug. Availability of off-label prescription presents profound personal and public health risks. The fringe physicians who now promote GHB will be joined by thousands of mainstream physicians with the approval of the FDA. The majority of physicians are ignorant of the diverse health risks of GHB, as are toxicologists and law enforcement officials. Users will seek Xyrem from physicians

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who don't recognize sodium oxybate as GHB and are unfamiliar with the health risks. Patients will obtain prescriptions for sleep disorders, also for insomnia, depression, anxiety, treatment of alcohol and drug dependence and other conditions for which it has been touted.

We know that addicts often use GHB and its analogs interchangeably. Their compound of choice is dependent on access, determined by cost, perceived quality, ease of procurement. Clinical literature reports one user who spent $200 per day. That comes to $70,000 per year. Our patients report ingestion of up to a bottle every one to two days, coming to $11,000 to $36,000 per year. A Xyrem prescription will be a bargain for such users, who will then avoid the high prices, erratic availability and risks of supplement and solvent purchase. We know that many people are afraid to

buy or make their own GHB due to risks of contamination or errors of production. Xyrem, a pharmaceutical product of controlled quality, available by legal prescription, and with very little risk if found in their possession, will be very attractive. We know that users are watching for the release of Xyrem. Recreational drug sites

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post links to narcolepsy sites and publications about Xyrem. One hotyellow98.com, for example, instructs users "click here to find out when GHB will be released under the trade name of Xyrem."

DR. KAWAS: Your time is up, Dr. Zvorsec. Please finish. Thank you very much, Dr. Zvorsec. Our nest speaker is Trinka Porrata of California.

MS. PORRATA: I wish I had time to tell you the stories of 200 dead people that I know of, hundreds of rape victims and thousands of GHB overdoses, and About Caleb Shortridge, to whom our website www.projectghb.org is dedicated, about Matthew Coda and Joshua Parks to whom our GHB addiction hotline is dedicated. I wish I could tell you about Ben Croman, Mike Fox, Tyler Johnson and other young men from New Zealand to Sweden who either have or are right now considering suicide because of the withdrawal from this drug; about more than 300 people I personally know about who are horribly addicted to GHB, and who could each name at least one dozen people more just like them.

I have lived and breathed GHB since June of 1996 when I was first assigned to handle it for the LAPD. Four young men collapsed. Two literally died and were brought back to life by the

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paramedics. One thing was clear, people were dying

from GHB and it was being missed. It has been a heartbreaking five years, mixed with the privilege of learning more and teaching others to recognize the rape, overdose and deaths and getting rape victims into treatment and addicts help. It has been very lonely at times when the agencies who should care haven't.

DEA has reviewed and documented 71 deaths related to GHB but, basically, stopped counting once the drug was controlled, for obvious reasons. No one at FDA has ever expressed interest in these cases. My database now includes over 200 GHB-related deaths. In fact, Robert McCormick, of the FDA's Orphan Drug Unit, told me emphatically he did not care how many people had died nor were addicted to it because he intended to approve it anyway. Something is wrong with this picture. This is the most horrid drug I have encountered in 25 years as a police officer.

Much new has come to light during the past two years, none of it good. Around the world countries are just now awakening to their problems with GHB. Schedule IV by WHO is simply an awakening to the problem. As we speak, countries

are restricting it. France is backing away. England is struggling with it. Sweden has an unrecognized addiction and suicide problem. New Zealand tried it as a prescription drug and now realizes they screwed up royally. NIDA is currently releasing $2 million in research on this drug. This is not a time to be pushing it forward on an unsuspecting American citizenry.

You are here today to approve GHB, disguised as sodium oxybate, for use with

narcolepsy/cataplexy. Orphan's investors have been assured that you will do so. When the last meeting was cancelled the stock dropped 30 percent in frustration over it. You have not seen my videotapes of the day-to-day struggle of GHB addicts showing that GHB clearly gives previously healthy people symptoms that can only be described as temporary narcolepsy/cataplexy, just like the nine-year old you saw in the tape. Their heads ricochet off board room tables around this country. They break mirrors. They are cut up. They crash cars. They die and kill others. It is destroying them. Their wives are terrified of their husbands and have no idea what is happening. They are locked in psychiatric wards because doctors and

emergency rooms do not recognize GHB psychotic episodes.

There are no answers for them. So, how can you approve this drug for use? My addicts suffer alone, much as narcoleptic/cataplectic patients do. Many do not have insurance or their insurance will not pay for this drug that is not recognized as an addictive drug.

I am deeply concerned about the off-label use policy, enabling any doctor ultimately to prescribe it for any condition as I have no faith that its use will be limited to narcolepsy/cataplexy. Look at the chatter around Orphan about fibromylagia, a condition with vague symptoms for which a drug seeker could easily get a prescription. I know the vast majority of doctors do not realize that sodium oxybate, Xyrem, is GHB. I see no significant talk on the legitimate

narcolepsy websites about it, but the message boards where GHB addicts hand out are buzzing. In fact, the key figures in illegal GHB Internet sales were posting on the website www.xyrem.com.

There is very little drug diversion enforcement in the United States. Only a handful of agencies devote any time to this. It is a small

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portion of DEA effort. States are not prepared. They are not able to handle it. Therefore, Orphan's proposed voluntary -- key word, voluntary -- promises of distribution are frightening.

More importantly, the issue goes beyond diversion of Orphan's product to use of Orphan as a shield for possession of GHB in general. It would be unrecognized by law enforcement. Once in possession of that prescription and a bottle of Xyrem, the addict will be home free. There is no field test kit. All investigations of GHB are difficult. Encountering a prescription, real or counterfeit, and a bottle of Xyrem, real or counterfeit, the officer would have zero ability to identify it -- none; zero; nada.

To those who claim real GHB is safe and only street stuff is dangerous, poppycock. My addicts have used everything from European pharmaceutical grade to bad stuff. The unprecedented split scheduling of GHB was unwise and unenforceable. We were forced to accept it. It was political, not science. The people in the clinical trials have reason to obey; people in the streets do not.

If I were to convey to you but one

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thought, it would be that not enough information is

known about GHB to approve it for any purpose at this time, and certainly not appropriate for off-label use. Any approval at this point will trigger an absolute further epidemic of general abuse because you will create an aura that it is safe. I ask you please table this issue until the NIDA research comes in. Please do not make this mistake.

DR. KAWAS: Thank you, Ms. Porrata. Our next speaker is Matt Speakman from West Virginia. While Mr. Speakman is coming up, I just want to remind everybody I am not trying to be mean; I am not trying to be difficult, but we are trying to keep the public hearing section of this meeting down to under two hours and that will only happen if everyone sticks to their five minutes. We would like to let the committee get a chance to have some more discussions for everyone. So, we greatly appreciate honoring the time constraints. Mr. Speakman?

MR. SPEAKMAN: Thanks. I just wanted to say thanks. This is kind of a unique experience addressing doctors. It is really cool.

My name is Matt Speakman and I have

narcolepsy. I will describe very briefly my experience. I have cataplexy also. My first experience was in chemistry class my junior year in high school. The professor pulled out the liquid nitrogen experiment and was freezing flowers and flicking them, making them shatter. I got very excited and he called us to the front of the room and, on my way up to the front of the room, I felt my legs start to buckle. This was the first time anything like this had happened. I had had trouble

laughing a little bit because cataplexy sometimes has onset with laughter and emotion, but it wasn't very serious.

I eventually just realized that I was going to fall. So, I went back to my desk and collapsed on the desk with my face down in my arms, kind of draped over the thing. It was humiliating. I couldn't move. I was awake and aware and I could still hear the class kind of looking around and what-not.

This started to happen more regularly and I started to fall asleep during class. My grades started slipping. I had to stop swimming. I was on the swim team. Falling asleep in the pool is kind of dangerous. So, I quit doing that. Most of

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my teachers suspected drug use and I don't blame them.

But I managed to get into the University of Kentucky and I went there for a year. I was unable to meet friends and my grades weren't very good because I spent most of my time in my dorm room. I didn't make it to class very often; very hard to wake up. It is very hard to keep consistent notes when you are falling asleep all the time.

My parents weren't happy so they found, you know, I needed some other treatment. So, I went to a doctor in Cincinnati who was part of the study for what is now Xyrem. That was four years ago, and I am taking it nightly unless I pull an all-night study session or something like that. I don't have any withdrawal symptoms when I don't take it. I don't have any side effects when I do

take it. I sleep well. I have no cataplexy. I am here speaking to you right now and I certainly wouldn't be doing this without this treatment. I used to take stimulants and antidepressants to control the cataplexy, none of which worked; they just had nasty side effects. It wasn't very good.

Two weeks ago I graduated from West

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Virginia University with honors. I am looking for a job --

[Laughter]

-- and I am thinking about going to grad school. That is definitely on the bill, but I am going to need some money first. So, first things first. Right?

I understand all the concerns about the illicit use and that definitely needs to be addressed, but this drug is working for narcoleptics and, you know, I have a girlfriend and I have a life, and I live normally. A couple of years ago I got a job as a full-time camp counselor in Maine; drove there myself; had no problems. I read the review they gave me after the summer was up and it said, this guy has the energy of a small power plant, which was nice to hear after suffering from narcolepsy for a couple of years. So, I am happy. I am working on success, and I just wanted to thank you for giving me the time to speak with you and I hope you can work all this thing out, but my main point was that the drug is working for narcoleptics and I want to thank the Narcolepsy Network for paying for my travel arrangements and my hotel. I am not in any way tied to Orphan

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Medical. I don't care who makes it. I just want

to let you guys know it is working. Thank you.

DR. KAWAS: Thank you, Mr. Speakman. The next speaker is Charles Cichon, president of the National Association of Drug Diversion Investigators.

MR. CICHON: Good afternoon and thank you. My name is Charlie Cichon.

DR. KAWAS: My apologies.

MR. CICHON: No apology. The nuns never got it in grade school; nobody has ever got it right. I go everywhere from Ceechon to Chicken.

[Laughter]

I have a 16-year background in law enforcement, but for the last 12 years I have worked in the health regulatory field with the Maryland Board of Physician Quality Assurance, the state medical board licensing and regulatory agency for Maryland. But I am here today as the president of the National Association of Drug Diversion Investigators.

Established in 1987, the National Association of Drug Diversion Investigators, NADDI, was formed in Maryland, in Annapolis by a sergeant in the Ann Arundel County police department. Our

organization is a unique organization whose members are responsible for investigating, prosecuting and preventing pharmaceutical drug diversion.

NADDI has proven to be a valuable asset to law enforcement, the pharmaceutical industry and health regulatory professionals. NADDI principal activities comprise cooperative education and training in the specifics of pharmaceutical drug diversion, investigation and prosecution; the sharing of investigated information and

communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion; and the development of stronger effective measures to combat the problem of pharmaceutical drug diversion.

NADDI supports the safety and efficacy of the new drug application, NDA 21-196, Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptoms of daytime sleepiness for persons with narcolepsy.

NADDI is aware that in many reported cases the use of GHB has changed from homemade GHB to ingesting of industrial chemicals that convert to GHB in the body. (My car got towed away yesterday;

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I lost my other glasses. I noticed that when I was sitting in the back and I couldn't read my paper. So, I apologize.)

We are also aware that there are no known cases which involved Xyrem. Rather than consider the above issues as tangential, Orphan Medical has gotten involved, helping to educate and uncover solutions in conjunction with stakeholders such as NADDI. In fact, since November of 2000, an Orphan representative appeared at our national conference in Columbus, Ohio, and for the last several months has been involved in several states in multi-regional training with over 600 NADDI members.

Input has been sought regarding distribution systems that will minimize and identify potential diversion situations, allowing diversion investigators to more easily perform

their jobs. It is the job of the pharmaceutical diversion professionals to investigate potential diversion, however, Orphan is willing to cooperate with the appropriate local, state and federal agencies. Thank you.

DR. KAWAS: Thank you. The next one is Debbie Alumbaugh from Florida.

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MS. ALUMBAUGH: Good afternoon. My name is Debbie Alumbaugh, from Florida, and I am the surviving mother of Michael Tiedemann. He was 15 years old when he died. That was just over two years ago. The cause of Michael's death was aspiration vomitus and GHB toxicity.

Michael was a sophomore at a high school in Florida. He was a black belt in karate, and he was also an instructor. He had won several academic awards for reading, spelling, mathematics and music.

On October 1, 1998, Michael came home from school and asked if he could go to the show with his friends. It was unusual for a school night but we decided to let him go. We required Michael to bring home a progress report every week from school and he had brought one home and he was making A's and B's in all of his subjects. Before they left, one of Michael's best friends came into our home and they shot into Michael's bedroom. This boy was only in there for five minutes and when he left Michael was passing out within ten minutes of this young man leaving our home.

We found out 18 months after Michael died that when they left our home they drove three

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blocks and started to play a game of basketball on

the way to the show. Michael had the ball and was going for a lay-up, and when he came down he was unconscious. He lay there several minutes. His friends, not knowing what to do or recognizing the red flags, giggled and laughed. They scooped my son up and took him on to the movies. We understand Michael never saw the first five minutes of the movie. He passed out again.

When they brought our son home, my husband looked at him and he asked him, Michael, are you on something? Did you take something, son? He said, no, dad, nothing. Brad decided not to lecture Michael this late at night; he would talk to him tomorrow. Brad never got that chance. Michael died that night, alone in his bed.

The next morning, when Brad went to wake Michael for school he could hear Michael's alarm blaring. Michael had full intentions of getting up. When he opened our son's door he knew he was dead. The first thought that ran through his mind was to run, run out of the house and not look back. My son was on his bed, his eyes wide open, his mouth hanging open, his tongue swollen so much that my husband couldn't shut his mouth. He had dry

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vomit running down his chin into a puddle on his collarbone. His hands were in a clawed position where he had tried to roll himself over but couldn't. GHB takes away the gag reflexes and it paralyzes you.

We didn't know why Michael had died. None of his friends would speak up. It took 12 weeks for us to find out that Michael had ingested GHB that evening. It was the first and only time that this had happened.

In the last three years, in Florida alone, we have lost 207 young lives to these drugs. From 1999 to 2000 our numbers have more than doubled in Florida alone.

After several months after Michael died, he came to his father in a dream and said, dad it is wrong to destroy the body the way I have done. I need you and mom to go out and tell my friends and my generation of people my story, our tragedy. This put a burden on our hearts and we seemed to stop healing until one day Michael's father gathered up enough courage and strength and he made the first phone call.

We now go to schools all over and share our story with students about GHB, and the tragedy

of our family. Friday, June 1 our son would have been 18 and he would have graduated on that day. When we went to his grave one Friday, his graduating class had left white roses and the mascot for the graduation cap. We missed prom; we missed graduation because of this drug. Our voices have to be heard. Please investigate this drug. It is not safe. It is killing our children and it is not the pushers that are dying; it is our good kids that we are losing. Thank you.

DR. KAWAS: Thank you, Ms. Alumbaugh. The next speaker is Brian Hunter, of the Young Adults with Narcolepsy.

MR. HUNTER: Good afternoon. My name is Brian Hunter. I am the founder of Young Adults with Narcolepsy or YAWN. I am also a medical student at the University of Minnesota and a person with narcolepsy and cataplexy.

I would like to preface my comments today by disclosing that Orphan Medical has provided my organization with a minor grant and it provided a general grant to the Narcolepsy Network who has paid for my travel and accommodations to attend this meeting.

YAWN is the first youth-focused online

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narcolepsy support and advocacy organization. We work at the grass roots level to advance public awareness of narcolepsy on behalf of young adults and others whose lives are affected by this often debilitating sleep disorder.

As founder of YAWN, I believe I am in a unique position to comment on the issue currently under consideration by this committee. I do not, and have not used Xyrem for treatment of my cataplexy but as the representative of many young adults in need of an effective treatment for their narcolepsy, I am compelled to present my views on the risk management issues pertaining to the safety and efficacy of Xyrem.

Narcolepsy is most commonly diagnosed by the middle of the third decade of life, often 5-15 years after the onset of symptoms, the most dramatic of which is cataplexy. Excessive daytime sleepiness, combined with the impact of sudden attacks of cataplexy that may last from a few seconds to hours can be profoundly damaging to the interpersonal, educational and professional development of these young adults at an extremely critical point in their development. Although I am fortunate only to experience rare and mild attacks

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of cataplexy, I know others who are completely

incapacitated by cataplexy and have not, or would not been able to achieve their personal professional goals without a medication like Xyrem.

I submit that the risk for experiencing the negative impact of untreated cataplexy on the potential of so many young adults with narcolepsy is a serious issue that must be included in any discussion of risk management of Xyrem.

Xyrem offers a singularly important therapy for the 65-70 percent of young adults with narcolepsy who suffer with cataplexy. We must recognize the consequences of failing to approve Xyrem to treat the 1/1000 people suffering with narcolepsy. For example, after forming YAWN, I was contacted by the parents of a 16-year old boy, living in a small town not three hours away from the nearest city. This young man was bright. He did well in school, and was active in his community until his 12th birthday when he began experiencing severe episodes of cataplexy that lasted for hours.

When I first spoke to him on the phone he told me that his condition was so severe that he was forced to spend five days a week in a nursing home, and he is still there. What are the costs of

providing nursing home care in a public institution for a 16-year old boy for the next 60 to 70 years? By not adequately controlling his cataplexy, what are his chances for becoming a contributing member of our society? Unfortunately, this man's story is all too common. Unless something is done about the current environment of limited access to inadequate pharmaceutical therapies, the future of young adults suffering with cataplexy will remain bleak.

This, however, does not have to be the

case. In fact, a brighter future has been achieved by the lucky few who have participated in Xyrem clinical trials. They have become success stories. To these young adults with narcolepsy Xyrem has meant the difference between a life within an institution and having the opportunity to achieve their goals, free from the physical constraints of their disease. Xyrem has enabled many young adults, my friends, to earn their Ph.D.'s or become lawyers, doctors or to simply be good parents.

These are people who took Xyrem and couldn't have succeeded otherwise. Yet, there continue to remain thousands of other talented and capable young adults who have not yet had a chance to fulfill their dreams. They are the reason I

formed YAWN and why I am here testifying before you today. We can no longer afford to neglect the potential of so many young adults by failing to provide them with the only medication known to be safe and effective. It is our responsibility to protect their right to pursue a happy and productive life by having access to medications like Xyrem that will effectively treat their disease.

Thank you for allowing me to present these remarks to you today. I urge you to approve the NDA for Xyrem. There really are lives at stake.

DR. KAWAS: Thank you, Mr. Hunter. The next one is Joe Spillane.

DR. SPILLANE: I would like to also say thank you for an opportunity to speak to the FDA and to this committee on this important issue.

I work at Broward General Medical Center

which is a community hospital in south Florida. My experience with GHB is as a pharmacist and in clinical toxicology. I also teach as an associate professor at the College of Pharmacy at NOVA Southeastern University.

Our experience in the emergency department is very similar to what Dr. Dyer mentioned. We

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have a lot of GHB overdoses. We had 48 overdoses associated with GHB in 1999. That number increased by 60 percent to 77 in 2000. We have more GHB overdoses than ecstasy. We have more GHB overdoses than oxicondon. I think it is important that I just underscore the immensity of the problem associated with GHB abuse. Most of our overdoses come in with people who have altered mental status and, basically, they just need a short period of supportive care, airway management. Most wake up. Many of them -- and I think this is important to point out, many of them mention that somebody had given them GHB, put it into their drinks, and so forth. As such, the media an many people have advised don't accept a drink from anybody but the bartender. We had a bartender up in our ICU about a month ago, and when he did recover I spoke with him and he said, yes, I chronically use GHB. A lot of my friends in the beverage industry also do. And, I think we can understand what the potential problems could be with that.

We have also treated five withdrawal cases and, again, the numbers might not be that big but this is just one hospital and, since it is a difficult thing to identify, we are probably

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missing cases and I am sure there are cases missed

throughout the country.

There have been nine deaths where, in the estimation of the medical examiner in Broward County, a county of 1.6 million people -- nine deaths were caused by GHB and I think it is important to point out that at least one of those deaths was with GHB alone, with no co-intoxicants and no alcohol level.

I guess my major concerns are with the scheduling and some of the off-label prescribing issues, and the voluntary nature of this distribution system. I kind of just want to summarize briefly by saying I think there are four questions that are major concerns of mine and I hope this committee addresses those concerns.

The first one is, is it really wise to rely upon an essentially voluntary, supposedly closed-loop distribution system, designed by the manufacturer, to prevent diversion of an increasingly popular, highly lethal, addictive and abused substance?

My second question is, is it prudent to require very little governmental regulatory oversight of such a system when the strict

adherence to that system may not be in the best financial interest of the entity responsible for that strict adherence?

My third question is, is it responsible to rely solely on those with a vested interest in demonstrating little or no diversion to verify that little or no diversion is occurring? It is my understanding that that is essentially what we may be doing here. I think there was an example of how this could be problematic just in today's

proceedings. I certainly was under the impression by several people who spoke today that there was no diversion in the clinical trials. I think Dr. Mani, from the FDA, said that, indeed, there were some cases of diversion. So, I just think that is a potential concern.

My fourth question is does it demonstrate judicious foresight to establish a precedent for sort of circumventing existing scheduling and distribution processes, and couldn't such a precedent be used in the future to the financial benefit of pharmaceutical manufacturers and to the detriment of drug diversion prevention?

I would like to commend Orphan for their work and bringing a medication that they feel is

effective to those who could benefit from it. I think a mandatory, not voluntary, system of distribution, with adequate governmental regulatory controls and any restrictions on off-label prescribing would advance another one of their stated goals, which is reducing abuse and diversion. Thank you very much for having me.

DR. KAWAS: Thank you, Mr. Spillane. The next one is Ms. Mali Einen.

MS. EINEN: Hello, and thank you for the opportunity to speak before you today. I could tell you my story of my scars and bumps and bruises from my many falls from cataplexy, or I could tell you about my disappointment from having had to give up my career that I was dedicated to and loved, not to mention the loss of income and security. Instead, the part of my story I share with you today is the loss of the normal, everyday things

that most parents take for granted.

My name is Mali Einen. I am a single mother from California with narcolepsy and what is considered severe cataplexy -- and a lot of nervousness. As a person with narcolepsy, I was fortunate to be diagnosed fairly quickly after the onset of my symptoms. I was diagnosed at the age

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of 22 after first noticeable systems of narcolepsy, appearing at about age 22.

In the early years my cataplexy was triggered mostly by strong emotions -- a truly funny joke or my young daughter saying something adorable. As the years progressed, my cataplexy worsened, requiring less and less of an emotional trigger to cause a complete collapse -- unable to move or talk for seconds, sometimes even minutes at a time despite my daily medications.

As my daughter grew and my cataplexy worsened, I was unable to attend her performances, school programs or sports activities without several full collapses. My young, then seven or eight year old daughter would complain, why do you bother to come? You spend most of your time passed out. That is what she called cataplexy. I wondered would she ever understand that it was my joy for her success and my love for her that prevented me from participating in these milestones.

Several years later my daughter's simply relaying a story to me, excitedly, about her latest crush or her experiences with her friends would cause me to crumble, much like the film that Dr.

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Mignot showed earlier today. It dawned on me that

I had not only given up my experiencing anything that might involve positive emotion, it had become difficult for me to even participate as a spectator in my daughter's life.

During the years, I had been able to maintain success in my developing career as a money manager. My workaholic, nose to the grindstone withdraw kept me away from the usual office fun and water cooler moments, while allowing me to avoid embarrassing cataplexy. But this too had begun to erode. Although the various medications allowed me to keep my cataplexy partially in check, it seemed that my nighttime sleep became more and more disrupted, sleepy during the day, yet never able to sleep more than an hour or two at a time at night.

By 1996, my spotty nights of a few hours of sleep, my sneaking naps during the work day, and collapsing in exhaustion any time I sat still had affected my ability to continue to perform my job adequately. Long ago my daughter had given up on my being able to read her a story or to help her with her homework. My life had become dragging myself to and from work, attending to the basic needs of my daughter, while constantly working to

keep my emotions in check. There was little room for fun and interaction. Sole provider for my daughter and myself, I finally voluntarily left my job.

By this time I had become a complete slave to my next dose of medication to either control my cataplexy or to help keep me awake. The medications didn't make me feel well; they made me feel horrible, yet, I was their slave. I had never taken a back seat to finding better or best

treatment options. I tried no less than five to seven different antidepressants over the years with varying degrees of success, but each with such a cost.

Within a year after I had left work, I became aware of a new medical study through Stanford, an experimental treatment for narcolepsy and cataplexy. I started Xyrem. My life changed! After a horrific washout period when, unmedicated, I was faced with my inability to care for myself, let alone my daughter, with mere thought causing collapse after collapse, I found that Xyrem controlled most of my cataplexy and I was thrilled how the better quality nighttime sleep allowed me to feel normal, almost good upon waking.

Although not required by the medical study, I began to voluntarily decrease my daily doses of amphetamines. The better, less disrupted nighttime sleep allowed me not to be a slave to my next dose of stimulants in order to make it through the next several hours. I now go many days without stimulants at all, and other days take 5 mg or less of Dexedrine.

I not only began to be able to listen to my daughter's glee-filled stories of her day, I started to volunteer at her school. I could joke with the kids; I could even watch Kelsey smash a winning serve across the volley ball court. I must admit, occasionally a funny story or my evening interaction with my daughter still causes my facial muscles to slacken with a bob of the head, but my daughter now uses these opportunities to give me a hard time, knowing that I will recover in a second

or two and we will have fun and enjoy our life together.

I asked my now 17-year old, upon contemplating being here today, would you say my taking Xyrem has made a difference in your life? I had expected the usual teenage disinterested reply. Instead, Kelsey responded, as tears welled in her

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eyes, as much as I hate it sometimes, you are really a part of my life now; you know everything that's going on with me.

It is for this that I am truly grateful to Orphan Medical and Xyrem -- and I think I forgot to say my conflicts of interest.

DR. KAWAS: That is the only reason we are going to let you go more over time.

MS. EINEN: I am a shareholder of Orphan Medical and a number of other stocks of products that I believe in. Narcolepsy Network has generously paid for my air fare and accommodations, but they have not compensated me for my time, nor am I paid for the time away from my brand-new job back in the career which I had to leave five years ago.

DR. KAWAS: Thank you, Ms. Einen. Next is Ms. Sandra Jones from California.

MS. JONES: Good afternoon, ladies and gentlemen. My name is Sandra Jones, and I am from Los Angeles, California. My travel expenses are being reimbursed by the Narcolepsy Network. I am 50 years old. It was only 19 years ago that my mother truly became a mother to me, my brother and sister. Nineteen years ago my mother began taking

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what we now call Xyrem. Within a week after she

started taking this medicine we noticed the incredible change in her. She could cook dinner without collapsing to the floor. She could sit down and eat dinner with us without falling asleep. She could make a sound that we hadn't heard in a very, very long time -- laughter, and more laughter without falling to the floor.

She became a totally new person to our family. That was not the case nearly thirty years ago. She quit her career as a nurse for fear of how the disease might affect her care of her patients. She became sort of a recluse in her home and we grew used to seeing her sleeping throughout the day and staying up all night. She was afraid she would fall and bring embarrassment to herself and especially to her family. People just did not understand her disease. She once collapsed at a party and people dismissed her as being a drunk. My mother didn't drink. It was what the narcolepsy had done to her.

This is an evil, evil disease and unless you have witnessed it firsthand you cannot understand the horrible ways it affects a person's live. Imagine having a newborn child, my sister,

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and not being able to hold her for fear of dropping her. Imagine not being able to go to the grocery store for fear of falling in the aisle. Imagine not being able to read stories to her children because she would fall asleep, not us. Imagine not being able to drive a car for fear of collapsing behind the wheel. This was my mother.

But Xyrem changed all that. It was a difference between night and day and mother quickly rediscovered the joys that she had missed for

decades -- playing games with us, going dancing, going to the movies, celebrating family birthdays and holidays. The day-to-day tasks that you and I take for granted, she could finally do as a normal person. This was the mother that we had never known until Xyrem gave us her life back and her family back. I have seen the difference. I have lived the difference. Please make this valuable medication available to people who have narcolepsy. They and their children will see the change in their lives. Thank you.

DR. KAWAS: Thank you, Ms. Jones. That concludes the section of open public hearing, and I want to thank everybody who expressed their views, information and helped the committee keep sight of

all the issues here.

We will now reopen the questions from the committee to the invited speakers, sponsor and the FDA. In particular, I would like to focus on the presentations that we had right before lunch involving the epidemiology, adverse medical events and the sponsor presentations on risk management and abuse liability. So, who wants to start the questions from the committee with regard to some of those presentations?

Continued Committee Discussion and Deliberations

DR. SIMPSON: I put up my hand under false pretenses because I had just one question really --

DR. KAWAS: We don't like false pretenses around here!

DR. SIMPSON: It was really relating to the efficacy. I mean, a lot of the presentations we have just heard give the impression that the

cataplexy was, if not completely controlled, almost completely. Yet, when we look at the data we see that the median number of events at the end of some of the studies is about eight or so on drug. So, do we have any data about how many people actually had no cataplectic events?

DR. REARDAN: I think that this question

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was discussed to some extent this morning. It dealt with complete cataplexy --

DR. SIMPSON: No, no, I am saying do we have data on the people who were, quote, cured? Were there any?

DR. REARDAN: We have a slide on that, I understand.

[Slide]

DR. HOUGHTON: This is an example of the long-term data, and one of the problems with the controlled GHB-2 trial is that it may be too short. The reason that the time was restricted is because of the imposition of patients on placebo for longer periods of time. But that represents a picture of the long-term response in terms of percentage change. So, we have a control across all doses, demonstrated here for a 12-month period, around the 90 percent or better mark. Now, that doesn't mean to say people don't have any cataplexy, but it is certainly very significantly reduced.

DR. KAWAS: Dr. Katz?

DR. KATZ: Yes, we have seen this slide a number of times. I just want to remind the committee that this is open, uncontrolled, non-randomized data, not the sort of data that we

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would ordinarily rely on to draw any sort of

conclusion about effectiveness of any sort.

DR. KAWAS: Maybe the sponsor could show us some of this data from one of the randomized trials?

DR. HOUGHTON: We could show you the change in the GHB-2 study again, which is the four-week study.

[Slide]

The data is median change from baseline. We had a median incidence of 23.5 in the 9 g group, a change from baseline of 16.1. If we present that again as percentage change -- because, once again, it is complicated by the spread in the data.

DR. SIMPSON: I guess my question is if the median at the endpoint is 8.7, it means 50 percent of the people were above it and 50 percent were below. Now, how many were below, say, 1 or 2?

DR. HOUGHTON: Well, it depends on what their starting level was, and the conditions of entry were 3 cataplexy or more attacks per week. We did have patients with very high incidence. So, in terms of absolute numbers, that is a very difficult response. I am not trying to be evasive.

DR. WOLINSKY: The other piece of that

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data though that you presented and might be worth looking at quickly is the randomized stop component of the trial.

DR. HOUGHTON: Sorry?

DR. WOLINSKY: When patients were randomized to be taken off --

DR. KAWAS: The 21 study.

DR. REARDAN: Right. The question is on a-patient-by-patient basis, how many patients went from X amount of cataplexy to zero cataplexy. Is

that what you are trying to get at?

DR. SIMPSON: Zero or close to zero.

DR. REARDAN: That is in the data listings for the trial. We didn't bring individual breakout of the data. We brought summary information for the committee. I don't know if Dr. Mani has a recollection or Dr. Katz.

DR. KATZ: You don't have a distribution of how many events patients had? In other words, you know, X percent had two or fewer events; Y percent had between two and five events.

DR. HOUGHTON: No, we didn't break it down like that. I think the slide that you were referring to was the one that I showed with individual patient plots, and I can show you that

quickly.

[Slide]

That is just an example of absolute numbers. These were individual patients plotted. That was their incidence at the baseline, and that was some two years after this was conducted. That is the sort of response they got when their active treatment was withdrawn. That is the group in active treatment. So, in terms of just absolute numbers, that is just a snapshot. That is not a statistical presentation. It happens to be every patient that came from that original trial through into this trial, and I show it as individual plots. It is the best impression of individual patient data I can give you to answer your question.

DR. BLACK: Just a comment on that. In this section we do have placebo-controlled data and we have the number of cataplexy attacks on placebo

versus active medications after patients have been on treatment for a long period. Dr. Katz' comment is very good. The data that has been generated over the open label, though it does suggest there is a time course till optimal effect of at least two months, is open label. But this is placebo-controlled data, suggesting that the

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average there of cataplexy attacks per day -- I don't know if you have the numbers of that, Dr. Houghton, but it is very low during the time of treatment unless they are taken off and then on the placebo-controlled portion.

DR. KAWAS: I have a question for the company as well as probably Dr. Dyer. I want to hear both sides of why we heard such very different descriptions of the potential for withdrawal syndromes with this disorder. I recognize fully that the company has studied individuals with narcolepsy and it is possible that alone could comprise the difference, but we do have a very nice withdrawal study in study 21, which is not typically the case, and the findings that were collected from that are in fairly sharp contrast to the stories that we have heard from Dr. Dyer with regard to withdrawal syndromes, and I wondered if both sides could tell me what the difference was. Is it dose? What is the difference here?

DR. REARDAN; I will ask Dr. Balster, but I believe it is dose and frequency. Bob, do you want to comment?

DR. DYER: I doubt that we disagree. Clearly, in my set of patients and what we use

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nearly as a diagnostic parameter and which patients

we should admit, even though their early symptoms are mild, is the frequency with which they are using it. So, the kinetics of the drug show us a duration of activity around three or four hours. When these patients increase their frequency so that their body constantly is exposed to GHB, those are the ones that we feel become severely physically dependent and then go through this withdrawal syndrome that can have an onset within hours of discontinuing the drug.

DR. KAWAS: So, in your opinion it is frequency of dosing, not even the number of grams per day.

DR. DYER: As far as I can tell, it is frequency because if I take the sponsor's information, and for years I have spoken to the investigators that are doing this and they have said they have had no trouble. Their patients have a 12-hour drug holiday daily, which is two to maybe three times what they are calling a half-life for this drug. So, the drug is completely eliminated from the body for a time period, and the patients have that become severely addicted, all of them -- I mean, that is kind of diagnostic for the severe

withdrawal, somebody who is taking it every three hours around the clock.

DR. BALSTER: Yes, I agree completely with that, and maybe the analogy that would help you understand it would be the analogy, for example, with alcohol where really alcohol can produce a very significant physical dependence but you can drink it every evening with your meal and you won't become dependent because between that evening use and the next day it has cleared the body. So,

whatever physiological adjustments are necessary have corrected themselves. So, we are in complete agreement.

DR. KAWAS: Thank you. Dr. Katz?

DR. KATZ: Just as an extension of that, there was also the implication or the explicit statement that in some of those people who took it very frequently and ultimately, presumably, became addicted, they were compelled to take it more frequently. In other words, there was a tolerance that developed and they had to increase their frequency to get the same sort of pharmacologic effect.

So, I will just ask the same question that Dr. Kawas asked about withdrawal. We have heard

from the company that patients who have taken the drug for years and years and years don't develop tolerance; they don't have to increase their dose; they don't increase the frequency of self-administration. But, we are hearing that on the outside there are people in whom this phenomenon apparently does occur. So, I will ask the same question. Why the disparity?

DR. DYER: Again, there haven't been really good studies or anything scientific. It is kind of my thoughts or opinions but, again, it is accommodation because you are taking it around the clock. So you are accommodating. Also, in the patients that are taking it -- well, I don't know, they are not really patients -- in the people who are abusing it there is a lot of the feeling that if a little is good, a lot is better. They are taking it initially, these body builders, for this

growth hormone burst. So, they really feel like they are doing the right thing. So, there is nothing to have them diminish their dose or hold their dose as it is. Then, once they start taking it more frequently, the duration of the drug as it wears off in three or four hours, we think, gives them kind of a dopamine surge for which then they

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are going to feel a little depleted and want to take that next dose. Then there is also physical craving for that kind of high. They are awake and feeling that kind of high as opposed to the patients that are taking it immediately upon going to bed and then sleeping through this euphoric -- whatever the kids are trying to get that are abusing it -- if you can roll that into an answer.

DR. BALSTER: That is exactly the way I would see it too. Just to add one further thing to that, the way to look at tolerance, you have to understand that it occurs through different effects at different rates and in different ways. So, the therapeutic effect is one effect. The intoxicating effect is a different effect. And, commonly in abuse situations where persons are trying to maintain an intoxication, they have to escalate dose and frequency in order to do that, whereas the data obtained in these clinical trials, of course, is on the therapeutic effect.

DR. DYER: One other comment, in the alcohol abuse trials they did escalate their dose in more of a craving kind of manner. That was about 15 percent.

DR. KAWAS: Dr. Roman?

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DR. ENGEL: I would like to add something,

if I may, to this point that is based on the risk management system proposed by the sponsor. As you saw, the data collected by the specialty pharmacy will include dose by patient. And, because of that, the specialty pharmacy will be able to predict when is the appropriate timing for a given patient to have their prescription refilled. So, for example, there are patients attempting to refill too soon, so to speak, that will be identified and it will be an opportunity for the pharmacist to interact with the physician very quickly, before a patient might get into a situation like which Dr. Dyer is describing with an overuse syndrome.

DR. ROMAN: A question perhaps again for Dr. Balster. Is the pharmacology of GBL and 1,4-BD similar in animal experience to GHB? Number two, if there is a difference, did I understand correctly that GBL and 1,4-BD are not currently drugs of abuse?

DR. BALSTER: Well, the first question, pharmacological comparisons of GBL, GHB and 1,4-BD, these haven't been very extensively done. So, hopefully some of those NIDA grants that someone

was talking about will really take that question on. But let me say that in a number of those studies that were done to describe the pharmacology of GHB, in some of these studies actually GBL was administered to the animal with the view that it was a prodrug for GHB. I forgot who said it but someone said that so far as we know, all of the effects of GBL and 1,4-BD are really as a consequence of their conversion to GHB. I believe that would be the current state of knowledge about

that although it is imperfect.

Now, the question about control, in a sense, yes, all of these drugs are potential drugs of abuse because they can be taken and basically are active in the case of precursors with metabolites. So, yes, all of these are potentially drugs of abuse. Only one of them is a controlled substance and one of them, by congressional action of last year, became what is called a listed drug, and I could explain that to you or, actually, Dr. Sannerud would know better than I what exactly that means. But it essentially means that there is limited distribution.

DR. ROMAN: So, with GBL and 1,4-BD there is no control.

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DR. BALSTER: Well, as I say, for 1,4-BD, to my knowledge, there is no control. I need to step back a little bit from that because we could get into too long of a discussion about what constitutes an analog under the specific language of the legislation. So, it is possible for prosecuting attorneys to claim that one or another of these drugs are analogs of a controlled substance. The Controlled Substances Act, in a sense, regulates analogs. Now, 1,4-butanediol is questionably an analog, but that would be something that would be worked out in court. So, I am not trying to tell you that someone could absolutely, with impunity, sell 1,4-BD to children and say that it wasn't a drug of abuse because I am sure that there would be authorities and prosecutors who would try to do something about that. But in terms of the actual language of regulation, only GHB is a

controlled substance.

DR. SANNERUD: GHB is a Schedule I controlled substance. Butanediol and GBL are considered controlled substance analogs under federal law, which means they can be prosecuted, as GHB, with penalties and other things would apply if someone is caught trafficking, distributing or

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clandestinely manufacturing or selling these compounds as well. GBL is listed as a List I chemical, which means that there is record-keeping and registration required. There are no retail sales of butanediol, and there is a graph in here with the product. These are used in industrial uses. So, this comparison is really a little bit misleading. I don't know the numbers but GHB is not even marketed yet, so this number on production is only for clinical trials I assume.

As far as the GHB and Xyrem they are both GHB. There is no forensic analysis that is going to differentiate between the two. So, when samples are submitted to labs there is no way to tell if it is the product or if it is something that is made at home. So, for someone to say that there has never been any diversion of the product, there is no way to tell that because there is no way to differentiate between the two under forensic laboratory conditions.

Another question I wanted to address is the quota issue. Ms. Meyers brought up quotas for Schedule II compounds, the stimulants. DEA sets the quota, as it will with GHB as well. It has never been the case that drug has run out at the

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end of the year because the quotas are set too low.

If there is a problem with the drug manufacture the quotas can always be increased throughout the year, and they are done so on a regular basis. So, there has never been the case where a drug has run out.

DR. KAWAS: Dr. Mani?

DR. MANI: I would just like to touch upon the issue of drug diversion during the clinical trials once again briefly. Many speakers have asserted that there has been no evidence that Xyrem or GHB used in the clinical trials included in the database was diverted. That may very well be true, barring the one exception that I cited earlier, and I have no firm evidence to the contrary. However, I have gone through the NDA, reviewed the whole NDA, and I would be a little more hesitant in making that assertion, and I will tell you why, and that has to do with the way the drug was dispensed in the Scharf study which, as you know, occupied about 30 percent of the database in terms of patient numbers and about 70 percent of the database when you are talking about patient years of exposure.

What happened here was that patients saw Dr. Scharf in Cincinnati, at least for an initial

visit, and had an appropriate diagnosis made and were then enrolled in the trial and then went back to whatever part of the country they came from. Prescriptions for medication were filled based on their returning completed diaries. In some instances it appears, at least from my looking at the case report forms, that prescriptions were sometimes filled in advance or the diaries being returned, obviously to prevent the patient from running out of the drug. But the important thing

is that patients were not required to return unused supplies of medication prior to getting a fresh prescription, or to provide any formal accounting of how much medication they used or did not use. In the absence of any active surveillance of that kind, as I said, I would be quite hesitant in making the assertion that no medication was diverted.

DR. REARDAN: I need to make a qualifying statement here. We do not disagree with Dr. Mani. However, under the company's clinical IND, our patients under IND didn't begin entering trials until 1996. Patients were required to document their dose; to return their bottles. The bottles were all qualified by volume in terms of what was

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returned. The incident that Dr. Mani refers to, I believe, occurred in 1986, when GHB was available as a nutritional supplement and Dr. Scharf's trial, again, was clinical practice. There were a lot of issues on GCP compliance in that trial. We do not take responsibility for accountability of drug under Dr. Scharf's trial. So, I will just qualify that. Okay?

DR. MANI: I agree.

DR. FALKOWSKI: I have a question and it has to do with the fact that we are talking about a method of taking this drug where you take half the amount at bedtime and then you wake up several hours later, but don't really wake up, and take the rest of it. And, I am just wondering what would happen if you were confused. It also involves mixing it ahead of time to the right strength. I am asking this both to Dr. Dyer and the sponsor,

what would happen if someone took 9 mg at once? You know, if someone got confused and took it all at once, what would be the expected outcome?

DR. REARDAN: I had a number of questions about this at the break from a couple of members of the committee -- how do they make it up, and so on. It might be worthwhile to ask Patti Engel to go

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through that. The other point about narcoleptic patients waking up, maybe Dr. Black, you could comment on how they wake up and take their second dose.

DR. FALKOWSKI: Right, but my bottom line question is what would happen to a person who inadvertently took all of their dose at once, and I really insist on an answer to that. Thank you.

DR. BLACK: That question has been answered by patients who have taken inadvertently larger doses. As far as the waking up at night, the patients that are here could probably respond to that, but the overwhelming majority are awake actually before the four hours later on their own and they are fully awake. The medication is premixed so there is no mixing that needs to occur at that point. There are folks who have taken extra doses and there is more sedation that occurs with the extra duration and the period of sleep is longer with the higher dose.

DR. FALKOWSKI: Is the answer then increased sedation? Is that the answer to my direct question?

DR. BLACK: Yes, if the dose is increased there is increasing sedation and a longer sleep

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period.

DR. FALKOWSKI: Okay. Dr. Dyer, could you respond to that?

DR. DYER: It is my opinion that the dose would be around 100 mg/k and at that point you are going to have coma and some of the other side effects that we see in our club goers are very likely to be what you would see. So, vomiting and aspiration is a possibility. You know, the ability to hear and react to fire alarms, children, whatever, that is all going to be blunted.

DR. FALKOWSKI: Is it a possibility then that some of these people who may have double dosed would be in a coma but who would know, you know? Is that a possibility, sponsor? I mean, who is to know?

DR. BLACK: I think that the question is a good one, and what I might call deep sleep someone else might call a coma. But when we look at the brain wave activity of the folks with the higher doses, they have nothing in the EEG that would be consistent with straightforward coma.

DR. FALKOWSKI: But you didn't take EEGs on these people when they were sleeping in situations like this.

DR. BLACK: Well, we have done EEGs on the folks when they have been sleeping at the 9 g dose but not on double the 9 g dose.

DR. FALKOWSKI: Okay.

DR. KAWAS: Dr. Katz, please.

DR. KATZ: Yes, a couple of things. Maybe the best way to get at this if it is possible is to ask the company to show us any data that they have about what happened to patients who took, let's say, a single 9 g dose. I don't know how many

patients did that, but if there is data on that it would be nice to see.

So, I don't know, maybe you could look for that while I get to the second part which is, again, just another variant about the question we were talking about before, this perceived disparity between patients and non-patients who take the drug recreationally. We have heard again, not just in terms of withdrawal and addiction and tolerance but just in terms of serious adverse events, a number of the serious adverse events that we have heard about in the emergency room situation seem to have occurred at doses, presumably -- I don't know how reliable the dose information is in that setting, I am not sure, but presumably at doses that patients

routinely get and which they tolerate extremely well. So, I will ask the same disparity question again there.

DR. MIGNOT: I think you have to realize also that you are talking about narcoleptic patients who also experience daytime episodes of overwhelming sleepiness that sometimes lead to confusion, and there are a lot of horror stories about narcoleptic patients, independently of GHB, at any moment of their life where they can sometimes be in a risky situation just because they have what we call automatic behavior, this overwhelming sleep attack where they really don't know what they are doing, where they may be driving or doing something dangerous. I think that is also important to keep in mind. The danger of taking two doses at a time, if it is relatively well dispensed, for narcolepsy patients I think needs to

be put in perspective for their other symptoms.

DR. REARDAN: I am only aware of one case in our database. It was a patient who inadvertently took 18 g and I think, Dr. Mani, you are well aware of that. He did fall on his head. So, it is confusing as to whether it was a result of his 18 g dose -- you know, that was the best

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estimate we had -- or in the fall he hit his head, but he did end up being taken to the emergency department and did need supportive care. Oh, Bill is saying that was a normal dose. I am sorry, let me get him to clarify.

DR. HOUGHTON: Yes, I am sorry. That is one of the cases that we know very little about. It was a patient who was in the kitchen. There was a loud bang. His wife heard the noise and came in, and her husband was on the floor. So, we got no dose relationship to that event. We know nothing as to whether it is related to Xyrem.

The 18 g overdose was the patient who was supposedly sleepwalking, in the Scharf database, who supposedly then took 18 g on top of his normal dose and was taken to hospital and ended up on a ventilator.

Really, the best prevention we have of 9 g being taken together is the fact that the dose has to be made up into separate doses. The instructions to the patient are very clear. They make two doses up together, dilute it in the water; drink one when they get into bed and the other, in a sealed cup, put away. Now, if they took the second dose in ten minutes or two hours, we have

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not done that study and it is very dangerous to

extrapolate that sort of dosing. On one hand, I can quote the patient who took 180 g and was taken to hospital unconscious and walked out of hospital four hours later to be admitted to the psychiatric unit.

I certainly don't want to propose that as the normal pharmacodynamic response. We have not done a study that has escalated beyond the 4.5 g dose twice a night, and I think it is very dangerous to extrapolate. It is also very dangerous to extrapolate the anesthesia data or some of the data that Dr. Dyer talked about this morning. Doses were given up to 100 mg/kg intravenously. If we believe the bioequivalence data, the absolute bioavailability data, that is equivalent to at least 300 mg/kg as an anesthetic dose, and that would be the best dose relationship we could give to dose escalation. Again, without true data I am not prepared to extrapolate from that.

DR. KAWAS: Dr. Mani, do you still want the floor?

DR. MANI: Yes, very briefly, just as further evidence of how much individual variability

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there is in response to this drug. There is a subject who Dr. Houghton had referred to in his presentation this morning, a healthy subject participating in a pharmacokinetic trial, a healthy young subject who received a single dose of 4.5 g and afterwards became obtunded, developed obstructed respiration perhaps because of his jaw falling back, became incontinent or urine and stool, and took a number of hours to recover but did not need any special supportive care. So, even

a 4.5 g dose may not be entirely safe for everybody.

DR. HOUGHTON: That story is somewhat true but not quite accurate. The patient was easily arousable, walked to the bathroom after the event of passed urine, after resting back in bed had a normal sleep and, two hours later was awake and ate a normal lunch. So, again, I can't account for the degree of obtundation but that still represented the maximum single dose in our database. It was a single dose of 4.5 g after a 10-hour fast.

DR. MANI: Although those details about the patient being able to get up and go to the bathroom and eat her lunch, and so on, wasn't in the narrative that we have available.

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DR. HOUGHTON: We were collecting urine samples every two hours and I can assure you the patient was walked to the bathroom. She certainly vomited at the time.

DR. KAWAS: Dr. Leiderman?

DR. LEIDERMAN: Very briefly because Dr. Mani raised one of the points that I wanted to, but the other question I had for the sponsor and the sleep neurophysiologists here, do you think that in some of the differential response that we are seeing in the narcolepsy patients as compared to the subjects who become dependent, addicted, have overdose problems that there may be a role not only of the basic neurophysiology of the narcoleptic brain but, of course these patients tended to be co-medicated with stimulants, and what role do you think that might be playing in the narcolepsy population?

DR. REARDAN: Is the concern that stimulants would still be present on board when they take their nightly dose of Xyrem? Is that what you are after, or what?

DR. LEIDERMAN: Well, I am asking for your thoughts on, shall we say, the differential effects of GHB on the two populations, and one of the sort

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of clear differences, taking sort of the first cut, is that narcolepsy patients are co-medicated with stimulants generally, whereas the abusing drug population, if anything, is self co-medicating with other CNS depressants or using GHB at high doses alone.

DR. BLACK: I think there are a number of questions that surface. We have patients in protocols where they are wanting to remain on the protocols or wanting to be drug compliant. There are reasons that they wouldn't abuse in addition or outside of the fact of co-pharmacy with stimulants and so forth. So, it is hard to compare those two groups clearly.

I think the best we can do is speculate. We have a number of patients that were not co-treated with stimulants as well, that were on just Xyrem, and they didn't self-escalate the dose or abuse the agent either. I think the only way to do it would be to give high dose frequently to the narcolepsy patient population and see if they are similarly addictable, and then it would be also interesting to find out what percentage of the normal population is addictable as well. Obviously, those studies couldn't be done. But I

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think we can't compare the two and it is real hard

to try to extrapolate the information we have to do a comparison.

DR. KAWAS: Dr. Dyer, followed by Dr. Van Belle, followed by Ella Lacey, followed by the questions that the FDA has asked us to consider. In between, we will get a quick demonstration of the mixing.

DR. HOUGHTON: Could I just add one point of clarification to Dr. Leiderman's question? There were patients in all of the studies that were not on stimulants. In the GHB-2 study I think it was about 15 percent when we did a recent look at the database for Dr. Mani. So, there was at least a proportion of patients represented in the database that weren't on stimulants as concomitant medication.

DR. DYER: There was one study, I believe it was done in rats where amphetamines and then a second with caffeine, where those were shown to kind of be antidotal to GHB poisoning, where it prevents the rats' loss of riding reflex. So, there may be some of that issue if they are taking it concurrently. One of the other things about the disparity, where I don't see the disparity as being

so much is that the narcoleptics are taking their dose at night. We know pretty commonly from the surgical studies from what we see coming into the emergency room and from the adverse effects of the study, that GHB causes vomiting and incontinence. So, we are seeing that in both populations of patients.

DR. CHERVIN: Is anybody there?

DR. KAWAS: Yes, is that one of our phone consultants, Dr. Chervin or Dr. Guilleminault?

DR. CHERVIN: Sorry, it seems like we were completely cut off.

DR. KAWAS: Can you hear us now?

DR. CHERVIN: Just barely. If there is any way you can make this signal more than barely audible, it would be helpful?

DR. KAWAS: We can barely hear you but it sounds like we are going to have to get the AV people on it, if you give us a moment.

DR. CHERVIN: I do have questions if I have time to ask them.

DR. KAWAS: I know that you are on a timetable, so we will put you in the middle of the six-person pileup, if we could let the speaker that is going now finish though.

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DR. DYER: So, there was another study where they took the patients and the patients that they gave the dose to and then forced or tried to maintain themselves awake, those were the patients that became confused.

The other thing is that in our emergency department study where we were trying to verify our ability to predict GHB by toxidrome, we looked at patients that came in with a GCS score less than 8 that were spontaneously breathing. So, unlike most CNS depressants that cause profound coma, generally the breathing is still spontaneous and maintained. You see mild respiratory acidosis but it is not very common that these patients need to be intubated. So, it is not contrary to be thinking that a patient might be comatose and survive the night.

DR. KAWAS: Dr. Van Belle, while we are

still working on the audio, do you want to go ahead and ask your question?

DR. VAN BELLE: I just have a brief question with respect to age eligibility. Will this medication be available to people under 18 years old?

DR. REARDAN: The company has not

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specifically developed data for pediatrics, and I think this would have to be something we work out with the agency but, typically, a medication approved for adults is not denied children. FDA and Congress have tried to put incentives in to get sponsors to develop pediatric information. In addition, narcolepsy is not generally a pediatric disease. I don't know if either Dr. Mignot or Dr. Black want to comment further. Dr. Katz?

DR. KATZ: Well, generally speaking, unless there is a good reason not to, we would limit the age that would be at least included in the indications or in labeling or dosage administration to the age of the lower limit of the age studied in the trials. I don't know exactly what the youngest patient was in these trials.

DR. REARDAN: Bill Houghton is saying 12.

DR. KATZ: Okay, 12. Again, if there was one patient who was 12 and everybody else was 18 and above, we would say adults or 18 and above, that kind of thing. It is true that there is no prohibition, obviously, from a physician writing a prescription for a drug for a child if it is only explicitly approved for an adult. It happens obviously all the time. But one of the questions

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when we get to it with regard to risk management

and that sort of thing is if there were no children studied, or children studied below a certain age, do you think attempts should be made to restrict it in this case? So, you know, it is open for discussion.

DR. MIGNOT: To answer the question, onset of the disease is roughly between 15 and 25. That is really when the bulk of the patients are coming in, especially for cataplexy, and I think it is very important to treat them early. As there is more and more knowledge about narcolepsy being an important disease and being recognized early -- I think you have heard a lot of testimony about how important it is to treat them early so that they can go through normal schooling. I think it will be very important to not be too restrictive towards the lower age.

DR. KAWAS: Dr. Lacey?

DR. LACEY: Two questions, one regarding the packaging. With the packaging being in a bottle and it is child-resistant dosing, and all, but hearing about adolescents and their involvement with GHB, I wondered if you considered other packaging. In deciding on this packaging, did you

consider individual dosage packaging at all, and what happened with that?

DR. REARDAN: We considered individual dosing packaging for sure. We thought that was a greater potential for diversion as it is easy to take those individual doses. I think maybe you would get some reassurance if Patti Engel can go through how we instruct the patients to dose and what the controls are for that. Patti?

MS. ENGEL: Thank you. To the point of

individual dosing, we did speak quite extensively about that with law enforcement.

DR. LACEY: Yes, I am pretty convinced about the patient. I am more concerned about others in the household who are exposed to a bottle.

MS. ENGEL: Right. I will address that as well. On the individual dosing, law enforcement was concerned about small containers that could be stuck in a pocket or purse, or slipped in someone's drink more easily. One of the things I shared with you earlier is that the bottle itself comes with a child-resistant closure. What is difficult to see from this distance, but it is something called a press-in bottle adaptor. When the patient gets

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this, there is a little well, if you will, in there. Even if a child can get this lid off, you can't drink it down. What has to happen is there is a metered syringe provided. It gets stuck in here and the patient removes a metered dose. Okay? They then have two child-resistant dosing cups and these aren't fancy. We took them because they are CPIS tested for child resistance, of course, and they put it in, preparing both doses by their bedside.

Now, the dose itself is metered. This Xyrem, to be frank, is not good tasting stuff. It is sodium oxybate. It is very salty. Many people will dilute it. How much they dilute it really is to their taste. We did not want to cherry flavor it or anything like that that may make it more attractive to children. Okay? Does that answer your question?

DR. LACEY: It really wasn't the small children that I was concerned about as I was about the older, the adolescents in the household who can open it the same as I could. So, I guess your answer was that law enforcement was concerned about the small dosages just being put in a pocket.

MS. ENGEL: That is right. Remember,

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illicit use of Xyrem also falls under C-I penalties, like heroin or LSD. So, we will never be able to find a package that a 19- or a 21-year old will not be able to get into. What we do, however, is to educate the Xyrem patient on a number of occasions of the penalties should that occur. So, there is an element of patient responsibility with this.

DR. LACEY: Thank you. The second question I have is about the suicide attempts that were presented by Dr. Houghton this morning. That was in that list of adverse events I believe, and it has continued to bother me that we talk about it as a suicide attempt as though nothing else happened and I am just curious, I guess, in those attempts were some of the other adverse events also experienced by those persons who were suicide attempters?

DR. REARDAN: As you heard from Dr. Mignot, depression is very common in narcoleptics, but I will ask Bill to comment on that.

DR. HOUGHTON: In all the patients who attempted suicide there was preexisting disease. In terms of response to the dose taken, only one of the suicide attempts involved Xyrem, and that was

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the patient who took a very large dose, about 300

ml of the drug which is equivalent to at least 150 g, and he became comatose, incontinent of feces and urine, continued to breathe spontaneously, was found by his wife in the bathroom, transported to the emergency medical care, did not require intubation or ventilation, and walked out of hospital four hours later to be admitted to the psychiatric unit. I certainly don't propose that as the norm. There will be certainly unconscious patients at much lower doses. So, please don't think I am proposing that as the pharmacodynamic profile of the drug. But you asked me what the side effects of the suicide event were and that is the only data that I can give you.

The second suicide event that was not fatal did not involve Xyrem. One of the fatal attempts did not involve Xyrem at all. The last suicide attack in the bipolar disorder patient was a real pharmacologic cocktail involving benzodiazepines, opiates, a number of drugs and some Xyrem.

DR. LACEY: But for those individuals who did have the suicide attempts, they did not have other -- not with the attempt directly but other

adverse events also in their report?

DR. HOUGHTON: No. One of those was a lady who had a group of people to her home. She asked them all to leave early, and when attempted to be contacted the next morning didn't respond, and when her attentions were sought she was found dead in the home.

The second attempt was a young lady who took an overdose of buspirone and told her father immediately. Her behavior was normal to that

point. So, that is an example.

DR. KAWAS: Dr. Chervin or Dr. Guilleminault, can you hear us now? You guys are next in the line up.

DR. CHERVIN: Thank you. I have two questions. Please tell me if it has been covered and I just was not able to hear it, but I read in some of the material that was distributed prior to the meeting about comparisons of the therapeutic index or the therapeutic window for GHB to that of other drugs that are currently approved and used. I was wondering if perhaps Dr. Dyer or Dr. Falkowski or Dr. Balster could address that comparison.

DR. DYER: Is that the comparison of LD-50

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in rats?

DR. CHERVIN: I guess it was rats, and it was LD-50 and effective dose, and they looked at the ratio.

DR. DYER: The problem I have with some of the rat data, lethal dose data, is the deaths we see are often secondary to coma. It takes high doses to cause pure respiratory depression. We have some patients that idiosyncratically have a pulmonary edema, but most of the deaths are secondary to unprotected coma and loss of airway. So, I don't know that that would extrapolate or come from rat data at all. I don't think you would see that.

DR. CHERVIN: Is there any other way to get at the issue of is Xyrem going to be more dangerous than other drugs that are used carefully when indicated?

DR. REARDAN: Dr. Chervin, I have some data on LD-50 that will help. Oral GHB has an LD-50 on the order of 9000 mg/kg in rats, and about 3500 mg/kg in mice. The IV LD-50 is about a third of that for GBL and for butanediol it is on the order of 2000 mg/kg. If you look at the effective dose, we are in the range, I believe, of about

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50-120 mg/kg recommended for the narcoleptic patients. Now, that is just on an LD-50 basis. I don't know if Dr. Mani wants to comment on the therapeutic range, or Dr. Katz.

DR. KATZ: I don't think we really know. I am not sure if the animal data is relevant at all. And, I don't think we have data that, in a systematic, adequate way, explores the full dose response both with efficacy or tolerability. As you have said, you have done a trial where the maximum dose, fixed dose, was 9 g per night and, you know, we either decide that that was a tolerable dose or it wasn't. And, you have the dose response for the effectiveness, and that is all you have. As you acknowledge, you haven't explored higher doses so I don't think we really know, and I don't know how you would really get at the question of how the therapeutic window, if there is one, compares to other drugs that are in common use. Some drugs that are used, there is a belief that they have a very narrow therapeutic windows, and some are wide. I don't think you can say more than that.

DR. REARDAN: I don't disagree.

DR. GUILLEMINAULT: I have a question.

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Narcoleptic patients have hypnagogic

hallucinations. They may even shoot -- if a gun is available they may hurt their bed partner because they are keeping their hallucination. How much does Xyrem decrease hypnagogic hallucinations, which is a very significant side effect which may kill neighbors and may kill even bed partners?

DR. REARDAN: If I understand the question, Dr. Guilleminault, it is how much did Xyrem reduce hypnagogic hallucinations in our trials, and I guess my first response is the incidence was very low and we did not see a statistical significance in GHB-2. I don't know if Dr. Houghton wants to comment further on hypnagogic hallucinations.

Just while they are finding the data, it is fair to say that the incidence of hypnagogic hallucinations recorded in the four-week trial was very low. There was a trend towards improvement that certainly didn't reach statistical significance. There was a better representation in the long-term open-label study and we could show that but I am loathe to do so because I certainly don't want to claim it as efficacy. I think we will be able to find the GHB-2 data.

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[Slide]

DR. HOUGHTON: In the Lammers study there was a reduction from 0.87 hypnagogic hallucinations per night over the 4-week treatment period to 0.28 incidence per night, with a p value of 0.008. That is one set of figures.

DR. MIGNOT: Just to sort of expand on what you said, if only about 40-60 percent of patients we narcolepsy/cataplexy have hypnagogic hallucinations as their symptoms or sleep

paralysis, then obviously that must reduce the power for the trial because they have only about half of the patients they included who even had that symptom.

[Slide]

DR. REARDAN: This is a slide from GHB-3. I guess that is open label, I don't know if we want to go into that. What it shows is median change from baseline to visit number and out through 12 months. You see a median change in hypnagogic hallucinations, a reduction of 0.35 per day. Is that right?

DR. KAWAS: Dr. Penis and then Dr. Falkowski and then this committee will be looking at the questions that the FDA has asked us to vote

on.

DR. PENIX: I think we have to anticipate several different possibilities in the treatment of patients with any drug, and I am somewhat concerned about the fact that the effective dose of Xyrem appears to be the maximum dose available, number one. Secondly, in regards to the possible protective effects of stimulants on the side effect of sedation, and whether we should consider Xyrem as a monotherapy drug or as an adjunctive treatment, and the question I would like to ask -- I think Dr. Houghton may have presented this data of talked about it, of the 15 percent of patients who did not receive stimulants while on Xyrem whether there was a difference in the maximum dose escalation in those patients compared to the ones who were on stimulants. I am not sure if we can answer the question, but if there is data on that,

if there is a difference.

DR. HOUGHTON: No, we don't have data separate for those on stimulants and those not on stimulants. There was only about 15 percent in that controlled trial that were not on stimulants. So, we hadn't plotted that at all. Remember that stimulants are taken in the morning and usually the

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last dose at lunch because narcoleptics are really trying to sleep at night and stimulants really complicate that, and the half-life of the gama hydroxybutyrate is about an hour.

So, even after their second dose their plasma levels on awakening in the morning are extraordinarily low. So, a contribution of stimulants to change that is quite unlikely. We certainly didn't see an abnormal sleep response in the normal volunteers in any of the pharmacokinetic studies, except the one patient who became obtunded, and she was awake four hours later and ate lunch, and then went home that day. So, the only real suggestion of data I could give you in the absence or stimulants is the single dose response or the repeat dose response in the pharmacokinetic studies, and that certainly didn't appear to be different at all.

DR. BLACK: I would just comment on the notion of a potential protective effect with stimulants. With the traditional stimulants, they are relatively short acting and there is a phenomenon called rebound hypersomnia as the medication wears off -- well demonstrated in animals and humans -- where the individual becomes

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more sleep than they would have been had they not

taken a medication; often a problem for those with narcolepsy who are using those medications.

Rather than those stimulants keeping people more awake and less affected by the Xyrem dose, there is the potential for even greater sleepiness with that rebound hypersomnia. That has not been well explored, but I think it would be erroneous to assume that there is any protective effect from the traditional stimulants. From the longer acting stimulant, modafinil, sleep studies have been done to suggest that there is no impact one way or the other on sleep in terms of depth of sleep and so forth.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: I have to take issue -- well, I already did with the statement that Xyrem will not contribute to the public health problem of abuse of GHB-like substances because I think it will and I want to take just a few minutes to elaborate on why that might be something I couldn't cover in the confines of my 15 minutes as well as covering those other points.

I had occasion last week, in Philadelphia, to present at a conference on drug abuse addiction

professionals from around the country, and since I speak about drugs of abuse, when I got to GHB I said, so, tell me about GHB in your community. Having heard from 15 people from 15 distinct parts of the country on this, a common theme emerged and that had to do with the fact that people who were abusing it couldn't quite get the dosing right because they kept passing out. Passing out became sort of a way of life. I think in Dr. Dyer's data we even saw that as well.

This is a drug that causes people to lose consciousness and in some cases respiratory arrest. Well, I think this is particularly relevant because if dosing is the problem I believe that this will only make more attractive a predictable dose as a known entity in a prescription product. "Gee, I can get around all these dosing problems by getting the prescription."

I am also concerned that none of the sponsor's packaging that I looked at even mentions the word gamma hydroxybutyrate, or did I miss that? I looked for it; I didn't see that. That concerns me because, as we have seen with oxicodon, we know, for example -- and I think it is a good case, we know that narcotic addicts will seek out

prescription narcotics for predictable dosing and for predictable purity. And, we have seen an increase once long-acting oxicodon was developed -- we have seen an expansion in its prescribing not just for chronic pain but for the treatment of even acute pain. That plays out to the tune of 300,000 oxicodon prescriptions in 1998 and over 5 million oxicodon prescriptions in the year 2000.

What people have to do, what drug seekers have to do to acquire it is go to a doctor and feign pain. This happens with unsuspecting doctors and it is happening in all parts of the country.

Now, diversion of drugs does not occur by people storming with machine guns the one central manufacturing. It occurs at the patient-doctor level. And, I am very concerned about the possibility of folks who are having trouble. Again, this is a diverse population; it is not just

kids using drugs. This is weight-lifters, these are people seeking effects, going to a doctor and saying, gee, you can get around all that; just go to a doctor and tell him you are sleepy. Just go to a doctor and tell him you collapsed. This is really seriously my concern about this, and I don't think that these two issues are separate. This

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drug has a huge following.

DR. KAWAS: I would now like to focus on the questions that the FDA has asked us to vote on. Do you feel very strongly that your comments are necessary before that?

DR. RISTANOVIC: I am going to make a comment extremely brief. The comment is very brief because in today's time we know how to diagnose narcolepsy. So, there is no way, even if someone is trying to malinger, to be given a diagnosis without appropriate testing in the sleep lab. That is a prerequisite.

DR. KAWAS: Thank you.

DR. RISTANOVIC: That is all.

DR. KAWAS: The FDA has given us three questions that they want this panel to vote on, and a whole page and a half of other items that they would like this committee to discuss.

So, I would first like to ask them if it is acceptable to facilitate the discussion, can I make the decision to split the first question into two?

DR. KATZ: Absolutely.

DR. KAWAS: Thank you. It might be the only thing that gets done quickly today. The first

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question is going to be has the sponsor

demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? I am opening the floor for discussion on that. Yes, Dr. Katz?

DR. KATZ: Again, I think it is very important for us to hear a discussion about dose and which dose. I mean, I mentioned that earlier in my comments this morning, but if you could address that it would be very helpful.

DR. KAWAS: Absolutely. In fact, maybe I would like to facilitate this part because I think this is the easiest thing that is going to happen in the next hour. To my mind, there have been two pivotal studies that have suggested efficacy for this drug in relationship to cataplexy at the 9 g level. Maybe by making that not overly provocative comment we can stimulate discussion. Does anyone want to comment on the dose or the effect on cataplexy before we vote?

DR. FALKOWSKI: Is that the recommended dose? It is not. That is why I am sincerely confused because the study seemed to show efficacy at 9 g, yet, the recommended dose is something other than that and that needs explanation. I don't understand that.

DR. KAWAS: Any other comments? Richard?

DR. PENN: I was going to make it a motion so we would save some steps. I think it is very clear that what you said is a good summary of the case that, in fact, they haven't set the dose at 9. They have suggested a different dose regimen and that has to be looked into very carefully. But the one thing I think we all we agree on is your statement. I would, therefore, put it as a motion, since we are supposed to do a motion so that that

has been shown.

DR. KAWAS: Would you like to make a comment, Gerald, before we pick the motion that is about to be on the floor?

DR. VAN BELLE: Sure. Well, I think it is the issue of dose response that I am struggling with in this case in terms of the pharmacokinetic model. If you assume that there is a pharmacokinetic model that is dose related, I would say if evidence has been shown for an effect at 9 there is probably an effect at 8.5 as well. Well, where do you draw the line at that time, and I don't quite know where to do that. I think there is ambiguous evidence for an effect at 6 and one study showed that. So, if you want the technical

answer, I think there is only evidence for clinical effectiveness at 9 but that ignores, to my mind, the pharmacokinetic aspects of the data so I am struggling with this.

DR. KAWAS: Could we restate Dr. Penn's motion that this committee vote on whether or not there has been efficacy demonstrated of this drug for the treatment of cataplexy and, specifically at the dosage of 9?

DR. SIMPSON: This may be my ignorance, but when something is labeled, for example, that it is efficacious at a dose of 9, does that mean that a doctor would necessarily prescribe it at 9? He could prescribe it quite a lot higher, couldn't he?

DR. PENN: That is going to get us into the next thing, which is how this is going to be monitored. Because it sounds like we want to put an absolute dose limit and we don't want to allow

variability in the population. By the technical way we are going to allow this out, if they are going to be watching how much a patient can take, then is a doctor going to be allowed the latitude a patient more, and you are asking can they be given less? I think the answer is usually the doctor makes that decision. Everybody understands that is

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the mean does that you have to use but that doesn't mean your patient will respond to it. So, there is the latitude unless we put into force this voluntary program.

DR. KAWAS: I would like to focus this committee back on the questions or we will never -- well, we will have everyone on a plane without a quorum in order to vote on these issues.

The first question really isn't so much about safety and what a doctor will do, the FDA has just asked us have they demonstrated efficacy for this drug in either of the two indications.

DR. FALKOWSKI: I believe they have demonstrated efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. I think that is what their studies have shown us today.

DR. KAWAS: Okay. We will be taking a vote and everyone's vote is going to count. Are there any other comments people want to make before we put Dr. Penn's motion on the floor?

DR. SIMPSON: I really agree that they haven't necessarily demonstrated efficacy in treating cataplexy but really in reducing cataplexy.

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DR. KAWAS: Do you want to put your motion

on the floor again?

DR. PENN: The company has shown efficacy at 9 g per day using a 4.5 divided dose for treating cataplexy in narcoleptic patients.

DR. KAWAS: These votes are going to have to be recorded individually I think. So, can we start with everyone who agrees that the sponsor has demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? Please raise your hands now.

I just want to remind everybody that the voting members of the committee actually are sort of in the central part of the table, beginning with Dr. Simpson and then going around to Dr. Penix. All who agree the company has demonstrated efficacy for cataplexy, raise your hand.

[Show of hands]

How about if we go around and identify, and start with Dr. Penix for the record?

DR. PENIX: I agree.

DR. KAWAS: Just your name.

DR. PENIX: Dr. Penix.

DR. VAN BELLE: Van Belle.

DR. PENN: Penn.

DR. KAWAS: Kawas.

DR. WOLINSKY: Wolinsky.

DR. ROMAN: Roman.

DR. KAWAS: All the people who do not feel the company has shown efficacy for the treatment of cataplexy, please raise your hand and start identifying.

[Show of hands]

DR. SIMPSON: Simpson.

DR. FALKOWSKI: Falkowski.

DR. LACEY: Lacey.

DR. KAWAS: I think that was everyone, so no abstentions in that case.

Moving on to the next hard one, has the sponsor demonstrated --

DR. KATZ: Dr. Simpson and Falkowski, I believe in your comments you said you thought there was an effect demonstrated, or something, but the vote went the other way. I just want to understand.

DR. FALKOWSKI: Right, I believe that they have demonstrated that there is some evidence of efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. These studies have been conducted on people who were already on

stimulant drugs. We don't know about the cataplectic narcoleptics who weren't. So, I wanted to reflect what we actually looked at, the scientific evidence.

DR. KATZ: And, would that be the basis for your no vote as well?

DR. SIMPSON: Well, mine is really that they reduced cataplectic events. I guess my understanding of treating it is that they couldn't sort of cure it.

DR. PENN: May I just clarify? I didn't mean cure. My motion was not cure, nor did I say monotherapy.

DR. KATZ: Right. From the point of view of an effect, you know, that sort of language only being applied to a cure, the vast majority of things we treat and give claims for in indications are for symptomatic, non-curative treatment. So,

it is perfectly acceptable for us -- and I think it was implied in Dr. Penn's motion that to vote yes you wouldn't necessarily have to conclude that the drug cures it or wipes these attacks out, but just that there is a decrease in these attacks compared to the control.

DR. FALKOWSKI: And you can call it

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monotherapy but what the subjects were in these studies were subjects with the condition that were already under medication for this condition. So, to take that leap to say, well, therefore, if you have people with this condition who are not on stimulant drugs, does that follow? I don't believe it does.

DR. KATZ: We will take that under advisement.

DR. KAWAS: The next question, has the sponsor demonstrated efficacy of Xyrem for the proposed indication to reduce excessive daytime sleepiness in patients with narcolepsy? The floor is open for discussion on this point.

At the risk of putting myself back in the same place as last time, I would summarize what we have seen today with regards to excessive daytime sleepiness that there was one study, in a double-blind fashion, that showed subjective changes in sleepiness with the Epworth Scale, and that would be the GHB-2 study. The other study which is being held up as a pivotal study with regards to daytime sleepiness was the Lammers study, which is a small study. Otherwise, I feel that the evidence with regards to daytime

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sleepiness was very weak at best, in particular,

the only study that proactively made daytime sleepiness the primary outcome measure as well as using objective measures with the MSLT was, in fact, negative. All the other studies were open label. So, here I have a little more -- considerably more difficulty actually seeing that the sponsor has demonstrated efficacy for daytime sleepiness. So, what are the committee's thoughts on this? What are the committee's comments on this? Jerry?

DR. WOLINSKY: As I tried to point out before, I think this is such an enriched patient population for purposes of the endpoints that were studied, it is hard to know that one could generalize daytime sleepiness effects in a full population of narcoleptics. So, I agree that the data is weak and it is also in a very enriched population.

DR. KAWAS: I am not sure I understand. For clarification, enriched with what? You mean enriched for cataplexy?

DR. WOLINSKY: Enriched for cataplexy which is not present in all narcoleptics and is not always present at this frequency. So, I don't

think that we would know. I would not know as a clinical that if I had a narcoleptic with sleep attacks or daytime sleepiness but no cataplectic attacks whether I could expect the drug to work or not, and I saw no data to tell me that I could.

DR. KAWAS: Any other comments? Any other thoughts before we call the vote on this question?

DR. PENN: I move that the company has not provided information to prove that daytime sleepiness is affected by Xyrem, and I would make a

comment on my motion, that if the company sees this as an important thing they can do a post-approval study on that specific item and that would be appropriate. I was leaning at the beginning of this to think that there was too much need for full proof on an orphan drug that this might be the case and I was going to give them the benefit of the doubt, but considering the potential for abuse in patients who will say they are just sleepy and the regulatory problems with that, I think we had better be quite strict on this.

DR. KAWAS: Can you make that motion without the addendum?

DR. PENN: No, no, the addendum is just my comment.

DR. KAWAS: Good. Give me the short motion.

DR. PENN: They didn't prove their point.

DR. KAWAS: The language is has the sponsor demonstrated efficacy of Xyrem for the proposed indication to treat excessive daytime sleepiness in patients with narcolepsy? So, a vote of yes the way I just worded it would suggest that the company has shown efficacy, similar to the last vote. A vote of no would suggest that the company has not shown efficacy for that particular indication. So, all in favor of yes, the company has shown efficacy for the indication of daytime sleepiness, please raise your hand.

[No show of hands]

All if favor of no?

[Show of hands]

Let the record show that it was unanimous.

It might be the only time today.

DR. TITUS: And enter nine names please into the record.

[Drs. Penix, Van Belle, Penn, Kawas, Wolinsky, Roman, Falkowski, Simpson and Lacey voted against the motion]

DR. KAWAS: Now, the second question that

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the FDA has asked us to vote on is has the sponsor established the safety of Xyrem when used for the proposed indication for which substantial evidence of effectiveness has been submitted?

Now, given our previous vote, we are talking about substantial evidence for the effectiveness to treat cataplexy, and I want to go ahead and put in here that I think most of the committee members have been of the opinion that the substantial evidence is almost exclusively in the 9 g dose range. So, I think we are talking about has the sponsor established safety of Xyrem when used for cataplexy at a dose of 9 g per day, for the most part. The floor is open for discussion on this question.

DR. SIMPSON: Could one of the physicians put the adverse events that one can see in the 9 g in perspective?

DR. KAWAS: Let me let Dr. Katz and Dr. Mani answer the question. Dr. Katz?

DR. KATZ: Yes, this is why the dose which you think is effective is important. It might be useful, before you decide whether or not the safety has been established at 9 g, to have a look at what the total exposure at the 9 g dose is and whether

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or not you think that is acceptable, as a first

step, independent of whether or not it seemed to have been tolerated, with enough people at 9 g with sufficient duration. So, I don't know if the firm could put up a slide. I think Ranjit has an overhead.

DR. KAWAS: Slide 67 from the company, updated ISS database, summary patient exposure by dose. By my calculations we are talking about 60 years, person years of exposure on the 9 g dose from the integrated data set.

DR. MANI: I am sorry, I don't believe it is patient years, is it? It is the number of patients.

DR. KAWAS: Well, I calculated it because there were 13 patients who had been on it for 2 years or more and 34 patients who had been on it 12 months or more. So, it was just 2 times 13 plus 34. That is the way I cam to the 60 person year estimate. I actually didn't give them any credit for the 6-month exposure.

Actually, I have a question to ask of the company, do each years subsume the others? So, the 13 individuals who were in the 2-year category, are they also included in the 62 who are in the 6-month

category and the 34?

DR. REARDAN: Yes, I believe that is correct, Dr. Kawas, the 13 patients would be included in the 34, and the 34 would be included in the 62.

DR. KAWAS: So, the math is more complicated than I made it out to be, actually. It still comes to about 47 patient years of exposure by my calculation. I believe that the standard generally if it is considered acceptable is

considerably higher than that. Perhaps Dr. Katz would like to comment on that, particularly in the case of an orphan drug with a relatively small patient population.

DR. KATZ: Yes, the typical minimum requirements for an application for a standard drug that is not an orphan -- we will start there because we have such standards written, is at least 1500 patients total or subjects total, with at least 300-600 for 6 months for a chronic disease and at least 100 for a year. That is the standard ICH minimum data package for safety.

As you point out, this is an orphan condition. I guess the company estimates the prevalence of narcolepsy patients with cataplexy is

about 25,000 or 24,000, something like that. And, we had agreed prior to the submission of the NDA with the company that, because it is an orphan with a fairly small prevalence, that they wouldn't really have to have the full data set that a typical NDA would have, and we agreed that a total of about 500 would be in the ball park. It is understood that at least some significant percentage of those patients should be at a therapeutic dose because the safety accrued at the dose that is less than therapeutic isn't particularly contributory.

So, while I don't believe -- the company can correct me if I am wrong, but I don't believe we set in stone what would the minimum numbers be that would be sufficient for either 6 months or a year or total active therapeutic dose. I don't believe we signed a contract about that, but I

think the implication is that a big chunk of the data ought to be at therapeutic dose. So, I can't give you an absolute answer but I will throw it back to you and ask would you think that the exposure at the therapeutic dose that you have seen is sufficient to characterize the safety profile reasonably and that we could write labeling that

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would adequately inform prescribers about what the panoply of risks is at 9 g?

DR. ROMAN: Could that be solved with a post-release very strict follow-up on these patients, Dr. Katz?

DR. KATZ: We really have to be assured that the drug is safe in use at the time of marketing. We cannot rely on post-marketing data to say, well, we will find out if it is safe in use. We have to make a decision about whether it is safe in use as described in labeling, whatever that is going to look like, at the time of approval. There may be additional information we would like to have in Phase IV but the fundamental finding of whether or not it is safe in use must be made prior to approval.

DR. ROMAN: A second point that I would like to make is that probably you can say that up to 9 g per day, not that there is sort of the middle of the road -- probably it would be recommended to start with a lower amount and increase according to tolerance and effects, but it is up to 9 g per day. That is sort of the upper limit. It happens to be the most effective one and sort of therapeutic dose but probably you would

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like to start with the lowest possible amount.

DR. KAWAS: I think the company shares your interest, but my take on this is we don't want to put out there that a drug is efficacious at one dose and safe at another. I mean, I think it is incumbent on us to feel confident that both of those characteristics go with whatever dose we think is appropriate.

In response to your question, Dr. Simpson, and I don't know if I understood it correctly but you said what is the clinical significance, is that from the perspective of a clinical?

DR. SIMPSON: Well, that is part of it. Just speaking as a statistician though, the safety evidence isn't there with those kind of numbers, obviously. I mean, I think everybody knows that.

DR. KAWAS: I think that is really more the question that is on hand here --

DR. SIMPSON: Yes.

DR. KAWAS: -- because from the perspective of a clinical, this drug actually -- you know, if you didn't tell me what the drug was and just showed me ten safety profiles that have gone by this committee in the last decade, or whatever, I suspect this would look like one of the

best ones. Nobody died from it. No major laboratory abnormalities were detected. But it is very, very, very few subjects that we are talking about, and I think that is considerable concern to us.

DR. SIMPSON: There actually was one suicide which could be attributed to this.

DR. KAWAS: It still puts it in probably the best of the ten. Dr. Katz?

DR. KATZ: Dr. Racusin, on our safety

team, just reminded me of sort of a simple rule that we use to decide what sort of size of a risk you can cap with a given exposure, it is called the rule of thirds, but basically with a cohort of 60 patient years you could be comfortable with ruling out a risk of no greater than 1/20, which is --what? -- 5 percent. So, in other words, there could be a rate of 5 percent of something bad with a cohort of 60 that you would not have even seen in that cohort. So, just to sort of give you an idea of what sorts of potential risks are there that we might not have seen yet with this cohort size.

DR. VAN BELLE: Just a small correction, Dr. Katz. I believe that it should be 3/60, which is 15 percent rather than 20 percent.

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DR. KAWAS: Do we have any other comments before we give a shot at trying to vote on the safety?

DR. WOLINSKY: I very much share your concern about approving the drug at one effective dose and then saying the safety is really at a lower dose than what is effective. On the other hand, I do think that we have some reasonable data on the efficacy side that says that the dose ranged somewhere between 6-9 g is effective for a substantial proportion of patients, which we then give us not roughly 50 years of patient exposure but closer to 200 years of patient exposure.

DR. KAWAS: I agree with that comment, Dr. Wolinsky, but I really would want to point out that almost all of the SEs appear at the 9, not at the 6 range. So, you know, you are stacking the deck a little.

DR. WOLINSKY: I thought actually, as I saw the listing of the adverse reactions, they clustered in two modal distributions. One was at the high range and one was, surprisingly, below 6.

DR. KAWAS: Actually, maybe we will take a look at that. Could Xyrem put up slide number 70 for us, updated ISS database does distribution of

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adverse events?

[Slide]

I think that is what you are talking about. It is not a perfect dose response. I mean, something pops up in the middle, the 6 range actually in terms of SAEs at 12 percent for the 6 g dose.

DR. WOLINSKY: And if I heard correctly, and I don't know how they were distributed, at least some of those serious adverse events were cataplectic episodes.

DR. KAWAS: But even then, I mean, I would point out that we are talking about a 3-fold increase in discontinuations due to AEs in the 9 versus the 6. I mean, it is a 3-fold difference.

DR. WOLINSKY: I take your point.

DR. PENN: On the other hand, once again, that looks like a pretty safe drug to me when you are only talking about 15 percent of people dropping out for AEs, and the real-life situation is that these patients are going to be titrated up to the 9 and, as we saw from that graph of the unacceptable information from the standpoint of the study results, in experience over a number of years you can run patients certainly at lower doses than

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9. So, I think that should be influencing our

opinion of the safety data.

DR. KAWAS: Thanks. Dr. Katz?

DR. KATZ: Yes, I think the critical question here is not whether those numbers at 9 g are acceptable or not, although that is an important question, but to me the question is -- and you have certainly been talking about that, do you have enough experience to be comfortable at the dose you think is effective. I think, I mean my sense of what people are saying -- you didn't vote on it yet, but my sense is that you felt that at 9 g there just isn't really that much data. I don't want to preempt your vote, but it sounds like the general consensus was there wasn't enough data there -- forget about what the data actually showed, but there just wasn't enough to be able to be comfortable that we have adequately characterized the safety at 9, which is what we have to do. The only vote you took on effectiveness was effectiveness at 9 g. So, if you think it is useful to reopen a discussion about whether or not you think there is effectiveness at 6 g, and if you do, then you have considerably more exposure to think about. So, that is your call. I

mean, Dr. Wolinsky suggested that he thought there might be some evidence of effectiveness at 6. I don't know how the others feel, and I leave it up to you as to whether or not you want to reopen that question because if you do think there is effectiveness at a lower dose, it increases your N from the point of view of safety. So, I just throw that out.

DR. KAWAS: I actually think that is probably worth our doing. With regards to

effectiveness at 6 g, what are the thoughts of the committee? I will start by saying that I suspect that there is effectiveness for at least many patients at 6 g, partly for all the reasons that other members of the committee have said, but also because there appears to be a fairly prominent dose-response curve not only in terms of AEs but also in terms of efficacy. And, what isn't factored into a total dose is the levels of particular patients, the weights of particular patients or whatever, but the data shows me that at least a subset of patients appear to be responding at least in some of the trials to 6 g. Dr. Katz?

DR. KATZ: Study 21, the withdrawal study.

DR. HOUGHTON: That is the slide that I

would really like to show if I could.

DR. KATZ: The dose there was 50 mg/kg, is that correct? What was the distribution of doses in that study?

[Slide]

DR. HOUGHTON: This is shown here. There was an equal distribution of patients at the 6, 7.5 and 9 g and if you look at that paradigm of acute withdrawal, the response to placebo randomization is obviously very robust at 6 and 7.5 g, as it is at the 9 g. The problem with the GHB-2 study is that it is only a 4-week study and the slope of the line hadn't plateau'd at the end of 4 weeks. When we did apply that to open label, even though it was open label we still saw the maximum nadir at 8 weeks. So, if you then take a group of patients who have been on active treatment for a very long time and are then randomized to placebo, if you

believe that is a support for long-term efficacy then efficacy is supported at 6 g and 7.5 g.

DR. KAWAS: Would members of the committee like to comment on this data or any other data showing efficacy or non-efficacy at 6 g? Yes?

DR. SIMPSON: I do think that this trial, in fact, is very impressive. I just want to remind

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everybody of the caveat of this, that the people that you were looking at long-term exclude all those people who have dropped out for adverse events.

DR. KAWAS: I think that is a very good point. I mean, this was a study done in responders rather than just random narcoleptics. Individuals in this group represented probably are individuals who felt they were getting benefit or saw benefit.

DR. SIMPSON: And provided the drug is safe, then in fact this might be a fair rule to look at to say, yes, the drug is effective.

DR. MANI: I would just like to point out that these comparisons are not of randomized groups.

DR. KATZ: They are not randomized to dose.

DR. MANI: They are not randomized to dose.

DR. KATZ: It is obviously a randomized study. So, they are not randomized to dose in the sense of typical dose response. These are doses that presumably they had been responding to in open experience, and there is not as balanced across the doses, that is true. And, the numbers are quite

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small on each dose. On the other hand, you have

already decided that in toto it is a study that demonstrates effectiveness.

DR. KAWAS: I mean, I think even though we all recognize these are responders, the fact that a group of individuals on 6 g who, when withdrawn, showed this effect at least told me that there was a subgroup that did respond, as I said before, to 6. The question is how big is that subgroup, and when we are talking about indications and efficacy do we feel that on the whole 6 is a dose to which people respond based on all the evidence that we have seen so far?

DR. FALKOWSKI: And I would also like to say I am a little uncomfortable with the idea of saying that we have so many patient hours for most drugs but, because this is orphan status, we have it but we don't have -- Dr. Katz' remarks -- but we don't have any numbers. Well, that, to me, puts the sponsor in a difficult situation about, you know, what is adequate in trying to develop a new drug and it makes it very difficult for us here to try to reach a conclusion. Enlighten me, here.

DR. GUILLEMINAULT: Can we make a comment, as a sleep expert, on the issue?

DR. KAWAS: I am sorry, who is speaking?

DR. GUILLEMINAULT: Yes, can we make a comment on that issue as sleep experts?

DR. KAWAS: Please. Yes, you are on the air.

DR. GUILLEMINAULT: Okay. The comment that I want to make is that currently there is no drug for cataplexy which is at a fixed dosage. None. Because there is a certain amount of variability from patient to patient, and a patient,

for example, can respond at 20 mg of fluoxetine or 60 mg of fluoxetine. In general terms, it is unrealistic to believe that there will be a single dose which will control all cataplectic attacks for all narcoleptic patients. So, you have dose ranges, and I think that that is what these studies are showing. Looking at the data that you have, efficacy for some patients is at 6 or for some patients at 9. And, that is the clinical experience, 20 years of clinical experience. That is the best that you are going to get. So, your efficacy for some is 6 and for some is 9. All drugs used for cataplexy are like that. All patients respond following that scheme.

DR. KAWAS: Thank you. Dr. Katz, would you like to comment on Dr. Falkowski's concerns about the orphan status?

DR. KATZ: The only written rules that I am aware of which talk about numbers that are adequate, or are potentially adequate, for an NDR, or for a typical NDR, there are no numbers written down anywhere as policy or guidance.

So, as I say, had agreed that a total of 500 was appropriate -- we, the company and the division.

DR. FALKOWSKI: So they came up short.

DR. KATZ: Well, that is the question we are asking. There was, on our part, that at least a big chunk of that would be at a therapeutic dose. So that is why we are asking you whether or not you think it is adequately chararacterized.

I just want to make one other comment with regard to the 6-gram effectiveness and to ask the

company just -- should make this explicit, although I think Dr. Trout said it a couple of times.

In Study 2, the p-value for the 6-gram versus placebo contrast was 0.0529, or 0.053, I believe. That was including a correction for multiple comparisons given the three doses.

So you have one study which, basically,

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has a p-value of 0.05 at the 6-gram dose; right? And then you have what you have seen. So I just remind the committee of that.

DR. FALKOWSKI: And that was the four-week study, the GHB-2 study; right? Okay.DR. KATZ: i

DR. KAWAS: Any final comments before we take a vote on the sponsor establishing the safety of Xyrem when used for the proposed -- well, actually --

DR. SIMPSON: Would it be appropriate to do a revote on the efficacy?

DR. KAWAS: Not revote, but we can do another vote on whether or not the panel thinks that there was efficacy demonstrated at --

DR. SIMPSON: A dose between 6 and 9.

DR. KAWAS: Well, I think we will have to say either a dose of 6 or a dose of 7.5 or something like that.

DR. KATZ: Well, if you conclude it is effective at 6 and you have already concluded it is effective at 9, it would be sort of odd if it wasn't effective at 7.5. So, if you just want to vote it at 6, we will take it from there.

DR. KAWAS: Okay. We are voting on 6.

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Has the sponsor demonstrated efficacy of Xyrem for

the proposed indication to treat cataplexy at the dose of 6 grams per day? All in favor? All who agree that the efficacy has been demonstrated, raise your hand.

[Show of hands.]

DR. KAWAS: Let's start and identify yourself as we are going around.

DR. SIMPSON: Simpson.

DR. ROMAN: Roman.

DR. WOLINSKY: Wolinsky.

DR. LACEY: Lacey.

DR. KAWAS: All who do not feel that the company has demonstrated efficacy at 6 to treat cataplexy, raise your hand. Start identifying at that end.

DR. PENIX: Penix.

DR. VAN BELLE: Van Belle.

DR. PENN: Penn.

DR. KAWAS: And I am the lone abstention, I think.

DR. FALKOWSKI: Over here.

DR. KAWAS: Oh; and Falkowski. So we have a split committee for you on 6. If I vote, I break it. Actually, I am fairly convinced that there is

efficacy at 6. So Kawas.

Now, safety. We are now talking safety between 6 to 9. We are now talking about a lot more patient hours, patient years. The floor is open for discussion for safety between 6 and 9 grams a day.

DR. PENN: Can the company give us the number of patient years exposure 6, 7, 9, total because we can't do it from your data that we have seen here. How close to the magic 500 are you?

Patient years; excuse me.

DR. KATZ: Not patient years. 250 patients greater than six months, if I added that up correctly. That is without Dr. Scharf. This is now with, so the numbers are bigger. Without Dr. Scharf, I calculate about 250 patients for at least six months. Is that about right?

DR. VAN BELLE: I got 399.

DR. KATZ: Greater than six months?

DR. VAN BELLE: Yes.

DR. KATZ: At 6 and above? We can just split the difference.

DR. VAN BELLE: How many Ph.D.s does it take to add nine numbers?

DR. KATZ: I am not a Ph.D. I can't be

expected to. Can you put the slide back without Dr. Scharf?

DR. KAWAS: I come to about 150 patient years of exposure just looking at the individuals who were on at 12 months or more.

DR. REARDON: This is the data without Dr. Scharf included from the ISS.

DR. KAWAS: I think it is important that we know exactly what we are looking at so thank you for pointing that out to us. On the other hand, I will say that it is to -- my personal impression was that Dr. Scharf's data, although it was the most extensive and the longest term, was collected the least systematically. Given some of the other issues that were brought up about it, it is probably to your advantage to stick with this dataset in terms of AEs.

Okay; then the vote is about to be called

for. If the sponsor has established the safety of Xyrem when used for the proposed indication at the dose of 6 to 9 grams per day. All who think yes, raise your hands.

[Show of hands.]

DR. KAWAS: Wait a minute. Something very funny just happened here. It seemed like more

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people were willing to say it was safe at 9 than are willing to say it is safe at 6 to 9? Let me try again. Who thinks it is safe, raise your hands now.

[Show of hands.]

DR. KAWAS: Identify yourself from that end.

DR. ROMAN: Roman.

DR. WOLINSKY: Wolinsky.

DR. PENN: Penn.

DR. KAWAS: Kawas in there. Anyone else? Who does not think it is safe, raise your hands, that safety has been demonstrated, established safety at the dose from 6 to 9 raise your hand now?

[Show of hands.]

DR. KAWAS: Has not been demonstrated to your satisfaction. Falkowski, Simpson, Lacey, Penix? Anyone else?

DR. VAN BELLE: Van Belle abstains.

DR. KAWAS: And one abstention. We are really helping a lot.

DR. KATZ: I didn't count. Was that a split?

DR. KAWAS: Right down the middle. Really helping.

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The third question that the FDA has asked

us to consider is the adoption of a risk management plan necessary for the safe use of Xyrem. I would like to focus us on that question. First, in a yes/no way rather than the details of whether or not, of what belongs in a management program if we think yes, or what doesn't belong if we think yes.

DR. FALKOWSKI: I thought part of our discussion was going to be different elements of that.

DR. KAWAS: That is the next part. First, let's decide do we need a risk-management program, yes or no. And then, if we do, what should be the elements. Jerry?

DR. WOLINSKY: I think there are really two issues here. I wish there weren't, but there are two. One is the risk-management program and whether it is critical for the patient population in which the drug seems to be indicated. I actually don't think that is important.

Then the question is is there a risk-management program that is necessary for the concerns about the societal risk at large. There, I think the answer is absolutely yes. Because of that conflict, we may be in an unusual position if

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we favor this drug, favoring, potentially, making a precedent step in which we put unusual controls on physicians and patients, more so than we have had in the past.

I am not sure there is anything wrong with that, but I am not sure that this is a large enough forum in which this question should be addressed.

DR. KATZ: There certainly are precedents for risk-management programs being necessary for the safe marketing of the drug. I don't know that

there are many, but there are certainly -- and I think you heard about some. So there is this precedence for a risk-management program.

Now, the details--I don't know specifically which details you are thinking about--may make this more of a precedent. But, certainly, risk-management programs of this type or similar type have been used and have been approved.

DR. WOLINSKY: I don't disagree with that, but I think we are talking about whether or not there is an inherent problem with the drug in terms of the efficacy, safety level that we are seeing. Most of the risk-management programs that I am aware of that have been put in place have been put in place for the protection of the patient not the

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protection of society.

DR. KATZ: Again, you have made a distinction which we have not yet explicitly made. It is a fair distinction. I am not sure everyone agrees that there would be no need for a risk-management program if it was just--if you weren't worried about the societal questions. But it is a fair point for sure.

DR. PENIX: Also, isn't it the difference in the fact that this is a controlled substance and the other drugs are not that the safety measures that are put in place for the protection of the patients are usually not controlled substances. So that may be a difference in this particular case.

DR. WOLINSKY: This is controlled, but I am not sure that the controlled substances have this much potential control on them is what we are suggesting here.

DR. FALKOWSKI: I have a question which is has the FDA ever been in a position where they have a drug coming before them that has already been scheduled? This seems to be unique.

DR. LEIDERMAN: Could I just answer a couple of these questions?

DR. KAWAS: Please, Dr. Leiderman.

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DR. LEIDERMAN: Let me refer you to a table. It is actually the last page in your blue FDA briefing package book. It actually lists several examples of risk-management plans for different drugs that come from different classes and for different therapeutic indications that are all in place for various safety reasons within the FDA, and they range from other controlled substances, potent opiates in the case of Actiq and fentanyl, to mifeprex and thalidomide. The risks and the intended protected individuals may be different in each case. Obviously, in thalidomide, the risk isn't to the patient but to the accidental fetus. Similarly, much of the consideration in Actiq, which is a potent opiate, was concern for other individuals within the household and, again, not for an opiate-tolerant severely debilitated pain patient.

So, to answer Dr. Penix' question, in fact, or Dr. Falkowski's, some of these have been already scheduled drugs. I think what is unusual but not absolutely unique is to start out with a drug that is basically in Schedule I and then to be bringing it into the therapeutic arena but, again, it is not entirely unprecedented either.

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DR. KAWAS: Thank you. I can't help but

point out that it is probably unprecedented, but this drug has gone from over the counter, a completely unregulated food supplement that could be bought by anybody ten years ago to Schedule I, which seems to me even more unusual.

So we are back to the question about the adaption of a risk-management plan necessary for the safe use of Xyrem. I think the comments that have been made, that Dr. Wolinsky made, was it may not be necessary for the safe use but it is necessary for other reasons.

Can we amend what we vote on, whether or not it is necessary, period, for whatever reasons and vote on it in that regard?

DR. KATZ: Yes; I would prefer you did, actually.

DR. KAWAS: Okay. The real question is is a risk-management program necessary. I have a feeling we are ready to vote on that. So I will call the question. All in favor say aye.

[Chorus of ayes.]

DR. KAWAS: No?

DR. PENN: No.

DR. KAWAS: Let the record show that Dr.

Penn voted no. Any abstentions?

[No response.]

DR. KAWAS: Dr. Penn, do you want to give your comments, since you were the descending opinion.

DR. PENN: I think this is a very complicated issue and I don't think we can resolve, at the end of a committee meeting, the responsibilities toward the general population of controlling the drug and the FDA controlling it for

a group of patients.

I see that the whole issue is being distorted in the same way that drugs for treating pain have been a problem and that is if we limit the drug with all these regulations, that the patient population, which is quite small, will not be served.

That certainly has been true with narcotic drugs over the years, that many, many physicians have underprescribed narcotics for a long period of time. I think we will see the same here except there won't be the same push to get it accepted by cancer patients. The narcolepsy group is much too small.

So it is going to be a very hard balance.

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I also worry about the idea of "voluntary" ways of doing this. They are not voluntary on the company. The company wants to get the drug out and they realize that they can't do it unless there are societal controls on the drug and they are willing to do it.

But I don't like the precedent of the drug company deciding for a physician whether, for example, somebody 17-years old will get the medication or whether somebody, because of different metabolism of the drug, might not be used on a slightly higher dose than 9.

Those are things that we have traditionally let the treating physician do and we have also not let the company choose who are the treating physicians. So I think this is something that needs a large amount of debate and that is why I was being obstinate and voting no on this without

qualification.

DR. KAWAS: Thank you. Rusty?

DR. KATZ: Just as far as the dose and the limitations, that is something that can be discussed in the context of what type of risk-management program you think needs to be in place.

You could have a risk-management program that

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doesn't say you cannot ever give a dose greater than 9 grams.

In a typical drug, when we have labeling, we have information that the drug is effective or safe only up to dose X, we don't usually say, "You can't possibly give any more." We just say, "Here is the data. There is no data above dose X."

So it isn't part and parcel of any risk-management program that you would automatically limit the dose. I supposed you could, but it is not presupposed that that must be the case.

DR. PENN: But you might limit age. The other thing is who is going to make these decisions. We were given this in the context of a very particular type of risk management. I think the devil is in the details in these types of situations and to vote yes or no is very difficult without knowing exactly what details we are talking about. They make major substantive differences.

DR. KAWAS: Let's go on.

DR. KATZ: That is why I wouldn't ask you to vote on the details.

DR. KAWAS: That is what I was going to say. Let's go on to the details. I want to remind the committee, particularly because of the lateness

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of the hour, if there is a detail that is not

important to you, please don't fill up too many of the airwaves with it so we can get to the ones that are important to you.

So the first one is should there be a requirement for additional safeguards; i.e., keeping drugs in a locked storage space in the patient's home. Just for a straw vote to begin with. How many people think that there should be the requirement for a locked cabinet in the patient's home? Anyone who thinks yes? Straw vote. Anyone who thinks no? Straw vote.

I think we have got a clear preponderance here. I think I will at least express my thinking is that we don't require patients to keep Demerol or Valium or Halcion or anything else in a closed cabinet, many of the drugs that are potentially at least as abusable as this.

Having said that, I think that almost all drugs belong in a locked cabinet. That is the real issue here and I am not sure to what extent requiring it would make one difference or another.

So, should there be a requirement for additional safeguards? Can I say, in general, that the committee felt that that was not essential, necessary.

Should there be additional warnings on the labeling of the dose cups and/or bottle? Any comments?

DR. WOLINSKY: I heard something that I thought was very insightful from one of the people who talked to us in the public session and that it would be useful if there was some distinguishing feature about the bottles that could not easily be counterfeited and this was be in everyone's best interest.

DR. KAWAS: Thanks. I assume that would be something that the company would do to the bottle rather than something the patient--

DR. WOLINSKY: I assume so.

DR. DYER: Are the dose cups to be labeled because those are not? So additional would be additional to that or additional to what is required by law, because they should definitely be labeled.

DR. KATZ: If I can just interject. I don't think there is anything required by law. This is what the patient keeps at home. Right now, I think they are just as you see them. There is nothing on them. There is no labeling of any sort; is that right? They are just blank?

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DR. KAWAS: Would the company like to comment? Is any additional labeling planned for the dose cups? Or maybe it is about to be planned for the dose cups?

MS. ENGEL: Actually, no. As you know, the poison-control system nationwide is going to a central 800 number as well as having a logo that is "Mr. Yuck" like but better tested for kids. That we expect to be ready in October. At that point, the central pharmacy will put into each of the packages three stickers, one for the bottle and one for each dose computer that will include that "Mr. Yuck" type symbol plus the central 800 number for the entire poison-control system nationwide.

DR. DYER: My concern is that if the bottle ever leaves the little dose caps--if you go away for a night, I am going to take my two doses with me. If they are separated from that bottle,

no one is ever going to know what it is.

MS. ENGEL: As I said, there are three of those labels that will go, so one for each--no; it does not.

DR. DYER: It needs to say what it is. If you go stay at a friend's for the night and you have narcolepsy and you take those two bottles with

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you, child-resistant caps are designed to keep children out for one to two minutes. That is it. Somebody will get into that and, if they do, there is no way to know what it is.

When they call that number to the poison center, they say, "I have a bottle with a "Mr. Yuck" sticker on it." It needs to say Xyrem and now many milligrams.

DR. KAWAS: I would like to call the question. Should there be additional warnings on the labeling of the dose cups and the bottle of GHB? Do I need to separate those two out or can I put the dose cups together with the bottle.

Let's start with should there be labelings on the bottles. All in favor raise their hands?

[Show of hands.]

DR. KAWAS: Is that almost unanimous? No? Labels on the dose cups saying that it is Xyrem or GHB or something. That is unanimous, please note on the record.

How about should there be additional warnings on the dose cups and/or bottle of GHB? I am not sure, maybe I should ask, what is the definition of additional? What is supposed to be on there already? Dr. Katz?

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DR. KATZ: I think we are probably mostly

thinking of the cups. There was supposed to be nothing on cups. So anything you put on is additional. I don't know about the bottle. I don't know if we were thinking specifically about the bottle. I assume that has all the usual required statements, whatever they are.

DR. KAWAS: Are you satisfied by our vote that there needs to be labeling on the dose cups? I think, though, I am starting to feel from the committee that there is some expression of wanting certain kinds of warnings added? No?

DR. DYER: If I could just add in, by law, you have to have "Keep out of reach of children," "Don't take with depressant drugs," "Avoid hazardous machinery." So those kinds of standard things would be on there and I don't know that anything else would be required.

DR. KAWAS: Dr. Lacey?

DR. LACEY: If this is a scheduled substance with implications for--legal implications, why wouldn't we put that type of warning in as few words as possible there. Maybe it would deter someone.

DR. DYER: There is already a requirement

for "Federal law prohibits dispensing of this drug to other than who it is prescribed." There is already a label like that required on prescriptions.

DR. PENIX: It could also attract certain people as well, I think.

DR. KAWAS: Yes; these warning labels have a mixed response. Can we move on to special concern or advice regarding limitations on the quantity supplied at any one time. Perhaps the

sponsor can correct me but my recall is that it is going to be dispensed at one month and then--a maximum of one-month supply at a time? Is that correct?

DR. REARDON: We had proposed to the agency initially to start at one month with each patient. As the patients and pharmacists get experience, that might be extended to three months or could be kept to one month.

I think the FDA is asking should there be a regulatory or legal description on the length of period that a Schedule III drug should be prescribed.

DR. KAWAS: Rusty?

DR. KATZ: I am not sure we meant that

question to be generic with regard to any Schedule III. We want to know whether or not, in this particular risk-management program, there ought to be a provision that says you only get one month at a time, or you only get three months at a time. We just wanted to know what you felt about that.

DR. KAWAS: The floor is open for discussion. First, do people think there should be any restrictions on the amount, period, and then we can discuss the timing. So straw vote. All people who think that we should be talking restriction of some sort or another raise their hand. And people who don't think we need to be talking restriction on length of time, raise your hands.

We have got a roughly split straw vote with the probable preponderance on the no time limit. Does that help enough?

DR. KATZ: Sure. If that is what you

think, it is helpful. I can't guarantee we will agree.

DR. KAWAS: Having worked in sleep laboratories as well as doing other physician things where certain drugs--I mean, my personal rule has been that drugs that have the kind of potential for trouble, of which there are many,

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many, many of them already in our armamentarium, I never give out more than one month's supply with three refills.

DR. FALKOWSKI: That is why I think that, particularly with this, we need to be cognizant of that and that there should be a limitation on that. That is all I wanted to say. And I also don't know where it comes in, or where this discussion happens, but I really believe that a drug, if you look at the third page from the back of the materials the FDA provided about just the scheduling criteria for drugs, that this drug, although it is efficacious for people with cataplexy, with narcolepsy or else on stimulant drugs, that it clearly--

DR. KAWAS: Your point it getting lost.

DR. FALKOWSKI: It should be in Schedule II. I believe it should have the dispensing restrictions that are more consistent with a Schedule II drug and I don't believe that would put undue burden on the patients because most of them are already on Schedule II drugs because they are on methamphetamines or other drugs.

Somehow, I wanted to say that today. Thank you.

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DR. KAWAS: Do you feel satisfied with

what you have heard on that question, Rusty?

DR. ROMAN: Claudia, one more point is how are the patients going to be selected. I think would should at least mention that the patient should have a clear diagnosis of narcolepsy with polysomnogram and MSLT

DR. KAWAS: You are jumping to Question 6, but why don't we go ahead and do that since I agree that is an important point and I am worried we won't get to it.

So what are your thoughts?

DR. ROMAN: That patients should have a recent polysomnogram followed by MSLT in order to confirm the diagnosis of narcolepsy.

DR. PENN: Who is going to decide whether it really is narcolepsy or not? The government? The company? The person who reads the test? The doctor that is taking care of the patient? That is why I mean the details are very important. You can say that it sounds good that we should have a diagnosis, but these are important points.

DR. KATZ: Can I just clarify what we meant?

DR. KAWAS: Thank you.

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DR. KATZ: We meant the treating physician, in other words, would make the diagnosis. We certainly, obviously, are not going to get involved in the diagnosis of a patient from where we sit. The company didn't anticipate that they would either if I can speak for them.

No; we just meant do you think that the patients have to have a bona fide diagnosis, does the physician who is writing the prescription have to assert, in writing, before the prescription will

be filled that, yes, this patient has narcolepsy.

Then you can throw this apart and say do they have to assert that the patient has cataplexy and that is what you have decided the effectiveness data supports. So that is a subtlety or nuance of the question you can get to. But specifically with regard to who is going to make the diagnosis, if you meant that question seriously, we meant the prescribing physician.

DR. KAWAS: Response to that? Dr. Roman, do you want to give your opinion and then Dr. Wolinsky has a question or comments.

DR. ROMAN: I think that there are diagnostic criteria that are sort of fairly well accepted, at least here in the USA. The question

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of should it be a certified polysomographer or should it be one of the certified centers in the nation, we will start getting into the problem of what happened with the patient who lives in the in the middle of nowhere and has no way to get to the next sleep center at 500 miles.

DR. KAWAS: Excuse me, but that is not what Dr. Katz asked you. He wants to know do you think the physician needs to certify, however they come to this decision, that the person has narcolepsy, that they need to certify up front, this person definitely has narcolepsy.

DR. ROMAN: One of the speakers mentioned that it is relatively simple to get a sleep attack and narcoleptic episodes that are real enough to fool the best unsuspecting doctor. So, since we have objective ways of making a diagnosis of narcolepsy, I think we need to use that for the

protection of the public at large.

DR. KAWAS: Thanks. Jerry?

DR. WOLINSKY: I think this actually frames what is my concern from before about protecting, or treating patients and protecting society. Now I want to get back more to protecting people who are treated. That really gets to an

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issue that we run away from in this country and that is, if we want to be able to push the envelope to be able to provide drugs that may be helpful for patients with true orphan diseases, we probably also have to say that we are willing to make sure that those people have what they say they have and that the drugs are being used in the context of the set of patients in whom they were originally tested.

It is one thing to talk about hemorrhoid cream but it is another thing to talk about a drug with a narrow therapeutic window and a diagnosis which can be made with accuracy by experts most of the time and could be misapplied by others a lot of the time.

This becomes a critical issue so that if someone is not willing to monitor this, all that we do, in looking at the hard science of what is presented to us, flies out the window as soon as the drug gets approval.

DR. HAGAMAN: Can I make one quick comment? I think, as a physician treating these patients, if they have had a PSG and MSLT in the past, there is really no need to bring them back in for another one. At that point, you have to trust

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the physician's judgment that yes, they do have a

diagnosis of narcolepsy, they have had the PSG MSLT done.

DR. WOLINSKY: I don't think the panel was questioning that at all.

DR. MIGNOT: Especially because, in such cases, you will have to stop medications which is another problem.

DR. KAWAS: I don't think that was being suggested. So let's move on if we could, please.

DR. SIMPSON: I don't know if this fits under it, but the way the question is worded, should there be restricted prescribing for the product. I just want to put in a plea for prescribing for children. As far as I can see, there have been no pharmacokinetic studies in children and children's pharmacodynamic and pharmacokinetic profile can be very different from adults.

So, given its complex pharmacokinetic profile, as it is, I would be very concerned if it was prescribed in children based, as is usual, on a way to a BMI.

DR. KAWAS: I am not sure that we have answered your question. Actually, I still have a

question that I want the committee to focus on unless Dr. Katz feels otherwise. Is it important that we decide whether or not it needs to be restricted to people with cataplexy as a component of their illness?

DR. KATZ: I am not sure whether or not you think you have made some sort of recommendation about whether or not it needs to be restricted to patients with narcolepsy globally yet. Do you think you have, because I didn't hear it if you--

DR. KAWAS: No; I don't think we have. You are talking now about certifying that the person has narcolepsy, at least on some signature level.

DR. KATZ: We did not put in how we you would know that the patient has narcolepsy. We anticipated that the physician would make the diagnosis appropriately. We didn't ask--I don't think we did anyway--about whether or not there should be specific diagnostic criteria that they have checked off or they have had a recent, or ever had a polysomnogram.

We anticipate, for purposes of this question, that the diagnosis would be up to the physician to make appropriately without any

additional specific requirements, but I suppose you could say patients must have a history of polysomnography and other tests, a multiple sleep latency test or an MPT before they can be prescribed this.

You could decide that you think that that is appropriate. We left it open intentionally.

DR. KAWAS: I think the committee needs to discuss that particular point. I want to make the comment, though, before we get too far, I would tend to leave it open and I recognize all of the things of modern medicine that all of the people in this committee are familiar with because we sit at major medical centers.

But there are people with narcolepsy and cataplexy at places that do not have access to sleep-disorder centers and polysomnography. I think that needs to be kept in mind or discussed on

some level as we are cogitating about this.

DR. ROMAN: The problem is that you need to go through the differential diagnosis of excessive daytime sleepiness and the differential diagnosis of cataplexy. In most cases, that is going to require at least a polysomnogram, a sleep test, to rule out obstructive sleep apnea,

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restlessness, and what have you.

So, in most patients, at least those who present for the first time to get this medication, I don't see how you can avoid doing these tests.

DR. BLACK: I hate to interrupt, but a point that I think is worth bringing up is that the condition indication here is cataplexy. Cataplexy is a clinical diagnosis not confirmed by any testing or MSLT. If you are going to limit it to cataplexy, I think it is important to recognize that you can't make any verification on the diagnosis with MSLT as far as the cataplexy goes.

DR. KAWAS: Since we have you up there, what percentage of people have isolated cataplexy without narcolepsy and sleep attacks?

DR. BLACK: It is incredibly rare.

DR. KAWAS: Thanks.

DR. BLACK: Incredibly so. But, on the other hand, the incidence of cataplexy and sleepiness without an MSLT that confirms it is a modest subset. In other words, if you have cataplexy, you won't necessarily have two sleep-onset REM periods on your MSLT, so we need to keep that in mind so that we don't potentially limit folks with true sleepiness and cataplexy and

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narcolepsy that don't show the MSLT findings.

It is not 100 percent specific or sensitive.

DR. KAWAS: We have some people over on this side who wanted to--

DR. LEIDERMAN: I just wanted to be clear about the question that I think we were asking. What was discussed internally within the agency was the concern about off-label use. We all know that drugs are used often more frequently for other than their labeled indications. The question we wanted to pose for this specific drug, does the committee recommend restricting its prescription to the labeled indication.

DR. KAWAS: So, actually, I think maybe, put in that context, we could call the question and try a vote here. In the opinion of this committee, are we recommending that this drug needs to be restricted in some fashion to on-label use? All in favor?

[Show of hands.]

DR. KAWAS: Almost unanimously. Negative?

[One hand raised.]

DR. KAWAS: One negative vote from Dr. Penn.

DR. VAN BELLE: I am going to abstain because I was out of the room.

DR. KAWAS: Dr. Van Belle is abstaining. Everyone else voted yes; am I correct? So, did we give you a better answer this time?

DR. KATZ: Yes. All your answers are good.

DR. PENN: Isn't this the first time anybody has ever suggested that the FDA should be restricting off-label use of drugs?

DR. KATZ: I doubt. I don't know.

DR. PENN: Isn't it stated in the FDA, all of your regs, that you do not regulate medicine and off-label use is up to the physician?

DR. KATZ: I don't know if it says we don't regulate medicine but, certainly, I think we have the authority to do, I think, plenty of things that some people might consider practice of medicine. So I don't think, as far as I know, there is any--as far as I know, there is no legal bar to this if that is the question you are asking. I think we have done it in the past.

DR. KAWAS: I think that I want to make the comment that even if it was the first time that the FDA was doing this, it certainly is not new to

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medicine. Now, insurance companies routinely make us do this.

DR. FALKOWSKI: I have one question, I guess, or one concern, and I just want clarification. Did I not read this correctly? I tried to read it all, but nowhere does it says gammahydroxybuterate. Is this correct, sponsors, that there is not the word gammahydroxybuterate in any of these doctor or patient things.

In terms of issues here, I think it is very important that the doctor information says what this is.

MS. ENGEL: As we worked with our colleagues in law enforcement, they urged us not to put gammahydroxybuterate as the generic name of the materials, et cetera, because they felt, for example, if you are a patient, and you have something in your home that says

gammahydroxybuterate, that might actually be an attractant to a babysitter or someone else.

So the attempt, based on the advice of law enforcement, was to separate that out.

DR. FALKOWSKI: I am not talking about patient materials--to the doctors. Will the doctors get to know? They don't have their

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materials sitting around their home.

DR. KAWAS: Excuse me. Dr. Katz, is this a question you would like the committee to discuss?

DR. KATZ: I think it is an interesting question. I think we can work it out. The point is well taken and, as the company says, they have gotten conflicting advice for good reasons as well. I think we can work it out.

DR. KAWAS: Great. Thanks.

DR. LEIDERMAN: I just wanted to respond to Dr. Penn's comment about restrictions on prescribing. Actually, there is some very recent precedence in the non-CNS drug arena. The drug, mifepristone, in fact, was approved under very restricted distribution. It requires signed documents by both physician and patient to be returned to the distributor before--and only a restricted group of physicians who certify to a certain ability to handle the complications are, in fact, allowed to prescribe the drug.

So that is a precedent in the non-CNS arena.

DR. KAWAS: I am told that somebody on one of our phone lines would like to make a comment? Can you hear us?

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DR. CHERWIN: Yes; I had wanted to make a

comment several comments ago, just to briefly reiterate. I agree with Dr. Black said which may be important that not all patients with cataplexy have positive sleep studies. So, in addition to, perhaps, in some cases, sleep studies not being available, this is another concern.

DR. KAWAS: Thank you.

DR. CHERWIN: Another thing is that cataplexy is not always a crystal-clear diagnosis. Not too many people have talked about that, but there can be cataplexy in the eye of one physician that does not exist in the eyes of another physician. That is a potential problem.

Finally, the International Classification of Sleep Disorders, which is to the sleep field similar to what the DSM is to psychiatrists, does not specifically require a sleep study diagnose narcolepsy.

I thought those three things might be salient to the discussion especially--since we sort of jumped to the appropriate prescribing section, maybe we can run through the questions there and see how many of them we can quickly comment on for Dr. Katz and the agency.

Should physicians document that they read the material sent to them before the pharmacy fills the initial prescription? If we took a straw vote right now, how many people would say yes? How many people would say no? Since we have got a split here, of the people who are on the yes side right now, would some of you like to comment on what kind of documentation you want?

I mean, are we talking a signature saying, "I have read the materials that were sent to me,"

or are we talking about something more than that?. Jerry?

DR. WOLINSKY: Again, it sort of depends what we require or what might be expected for a diagnosis rather than what would be required. I think if a sleep specialist is comfortable with the diagnosis in that patient, and refers the patient back to treatment to that physician who is back in North Dakota that you keep mentioning that can't possibly have all of the diagnostic tests around, then I think it is important that that physician in North Dakota knows what they have signed on to.

If it is the sleep specialist who has got 150 patients on treatment because they are very expert at this, if they have signed the document

once, that is probably enough for me.

But I think these are details that I am not sure that we need to work out today. There are plenty of things that can be worked out by Russ and his people.

DR. KAWAS: Russ and his people gave us this question.

DR. KATZ: And we didn't anticipate, necessarily, a vote. But right now, as I understand the program, the initial prescription is filled and then the physician and the patient have to send back a card that says, "Yes; I read this stuff." It was just some sentiment internally for all of that documentation that, "Yes; I have read it. Yes; I understand it," that is to happen even before the first prescription was filled.

We are going to get into major problems if we try and apply a different standard to different

types of treating physicians, the expert versus the non-expert. Actually, this was one of the issues that I actually did want. A lot of them are not necessarily that critical but this was one of the few that I really wanted some discussion on. There are a lot of other details I think we can take care of.

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DR. WOLINSKY: But I guess I was saying that, that even the expert would sign it. He just wouldn't have to sign it every time he gives out a new dose.

DR. KATZ: No, no, no, no. We don't anticipate that.

DR. KAWAS: Once.

DR. KATZ: I just meant the first time you give a dose to a particular patient, you would sign a card before the initial prescription was filled for that patient. That is what I think we anticipate.

DR. FALKOWSKI: On a patient by patient?

DR. KAWAS: I want to make the comment that I am comfortable with the notion of physicians having to sign for this potentially, but I am not comfortable with what was suggested as a mechanism to have it happen by the sponsor and that is sending a drug representative to the physician's office. I really feel very strongly that is not the way this should be done.

Dr. Penix?

DR. PENIX: This is a question for Dr. Katz. What is the purpose of the physician signing such a document?

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DR. KATZ: It is just to acknowledge that

they have read the material and that they are familiar with its safe use and that they have spoken to the patient about its safe use. Actually, that is a separate question, but it is all combined--that they know how the drug should be used, what its risks are, what the penalties are for inappropriate use.

DR. KAWAS: Doesn't it also sort of acknowledge that this is a somewhat unusual drug in some sense because every drug has all these risks in prescribing and we don't ask any physician to sign for all those drugs.

I sense on the committee a growing concern that the more drugs we have to sign for, the more uncomfortable they are becoming. But I think, really, it points out to the physician who is signing it that there is something different here.

DR. PENIX: I think, also, in that sense, it is important for the physician-information packet that they are aware that this drug is GHB and so, therefore, they may understand why it is required for them to sign this information.

I think that is really the bottom line. So I think it would be useful for a treating

physician to know what type of drug this is.

DR. FALKOWSKI: I would say yes only if it says it is GHB.

DR. DYER: Wouldn't CII make that implicit to know that this is a drug that has illegal implications and would be dangerous?

DR. KATZ: It is Schedule III.

DR. DYER: I am saying it belongs in Schedule II.

DR. KATZ: I think that question has been

dealt with definitively. It has been legislated as Schedule III by Congress.

DR. FALKOWSKI: Right. That was legislated at another time.

DR. PENIX: Not to belabor this, but I agree with that drug company's position not to let the patient information--or not include GHB in the patient information. But I think the treating physician should be aware of that.

DR. KAWAS: I think that is a very important point because physicians do have a knowledge base of GHB even if it is from the newspaper or whatever to insure that they understand what it is.

DR. ROMAN: It also has the legal

implications of a physician somewhere who has been prescribing this at a higher rate than expected for that population. He may find his licensing--and a problem if they find that he is prescribing more of these, let's say more than a couple of patients in a year, or whatever it is that delimits.

So we need to look into that because there is potentially a risk for medical licensing.

DR. KAWAS: Can we see if we have shifted the straw vote from about a 50:50 split to something that is more consensuslike for the agency? On the question, should physicians document that they read the material sent to them before the pharmacy fills the initial prescription, presumably, some of those materials would incorporate the fact that what this drug really is is GHB whether or not it is on the bottle.

All in favor?

[Show of hands.]

DR. KAWAS: Nos?

[Show of hands.]

DR. KAWAS: And no abstentions. So let the record show that nos were Dr. Richard Penn and Dr. Gerald Van Belle. The remainder of the committee voted yes. No abstentions.

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Should physicians be required to demonstrate safe use and appropriate dosage preparation to patients before the first prescription and be required to document that it has been accomplished? Do we want to try a straw vote and see if we can keep on going?

I think I will make the comment that patient education is too important and sorely underdone in this medical world that that is true for everything. I think, personally, that it would be the hope that, with all drugs, that the healthcare team will insure these demonstrations. I am going to suggest that we do not need to require any specific demonstration or any specific certification of this process.

I see some heads going in different directions. Let me get a straw sense on this one. Should physicians be required to demonstrate safe use and dosage? How many people are going to say yes? Straw vote.

DR. FALKOWSKI: Is the intent here that it just be demonstrated regardless of who does it, whether it is a nurse or a physician? What is your intent?

DR. KATZ: The intent was that--I don't

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think we necessarily meant the physician but

someone responsible in the physician's employ. It shows them how to draw it up and how much your dose is.

DR. FALKOWSKI: Should somebody demonstrate how you administer this drug before the patient takes it. So I think that is a good question. Can we take a vote on that?

DR. KAWAS: You mean someone in the physician's office should be required to demonstrate it and, in some way, ascertain it. The question is called on that. Who votes yes?

DR. VAN BELLE: Before we vote, there is a further addition to that statement here, and it says, "And be required to document that it has been accomplished." Are you intending to have that included as well?

DR. KAWAS: I think everything that happens in a physician's office needs to be documented. So, yes. That is why we are writing twenty-seven page H&Ps right now.

So we have got one vote yes? Is that all? Dr. Falkowski. No votes?

[Show of hands.]

DR. KAWAS: Abstentions.

[One hand raised.]

DR. KAWAS: We have got one abstention with Dr. Simpson and the remainder of the committee voted no.

DR. WOLINSKY: Having voted no on that in terms of the office personnel and the physician, it seems to me that it would be advantageous to the company to have first doses shown in the home when medication arrives. This is actually the effective education.

What goes on in the physician's office, my bias is, may not be as effective as with home nurse agents.

DR. KAWAS: I think we are not going to repeat the restricted prescribing for the drug question. We have gone over that adequately, I hope.

But the next one, does the risk-management program assure appropriate prescribing or sufficiently reduce the risks of misuse or overdose. I am not quite sure where to start with this one. Actually, Dr. Katz, which components of the risk-management program are you asking us to comment on?

DR. KATZ: That is a fair question. This

is sort of a global question, I think. To the extent that you have seen the details of the proposal, is there anything that leaps out at you as being absolutely inappropriate, or is there something that is not there that is a glaring omission that you all believe absolutely should be there?

I think that is sort of the sense of the question.

DR. PENN: Yes. I don't think the potential problems of the drug are explained to the patient adequately. That is, the narcoleptic patient won't necessarily know that this is an abused drug or if they take it in the wrong way that they can get into a lot of trouble and that the real education has to be to the patient in some manner.

I usually think that is the responsibility

of the physician to do that, but I don't see that--I mean, we are protecting the patient from knowing what the name of the drug is. We are protecting them from knowing what the real side effects might be.

It doesn't say that if you take double the dose, it may have more than double the effect and

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that you may go into coma and become incontinent and have seizure--well, probably not seizure but stop breathing or something unpleasant like that.

I think the emphasis should be on the patient understanding the medication and how to use it. The narcoleptic community suffers enough and has pretty good ways of letting each other know about the disease. Maybe you should use their ability to instruct patients on the proper way to do it and combine it in some way.

But that is where I think the glaring error is. This is a drug with very little leeway for dosing and people have to understand they shouldn't use it during the day, for example, because they won't have this period of time off.

So I think there is a huge amount to be done. I just don't like to see it done in this mandatory fashion because I don't think it will work. You will get a lot of signed papers, but you won't get the education you need done.

DR. KATZ: But I just want to clarify. I understand your reservations about the entire process but, given that there is a document that goes to the patient that ostensibly tells them what they need to know about using the drug safely, you

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believe that that document that is currently

written really needs to be beefed up as far as communicating to the patient what the risks are and how to use it?

DR. PENN: Yes; I think that the patient has to know what it is, that it is an abused substance that potentially can be abused. It would be like our not telling patients who use oxicodon not to chop it in two and take it. That gets them into trouble and they ought to know about that.

So there is a lot of education that has to be done with this medication.

DR. FALKOWSKI: I think I already addressed this question by saying I think the word gammahydroxybuterate should appear for patients and particularly for the physicians, the prescribing physicians. What is the secret? The way to have a drug come into the market when it is already a substance of abuse is not to pretend it doesn't exist and not even call it what it is.

I don't think that is an informed approach for physicians to know what it is.

DR. LACEY: Just as one presenter, and I don't remember who, today gave us the common names, the club names and everything. I think the patient

actually should be provided with as much of that information as possible. To not want to put it on the printed book or something because it is exposed to someone else is one thing. But the patient should be provided as much information as possible to know what they are dealing with.

DR. KAWAS: Any other comments before we move on to the next question? Jerry?

DR. VAN BELLE: Let me just make a comment. I agree with that and, also, from the

practical point of view, we have already heard this afternoon that the narcolepsy website network is just far flung. If this is going to be approved by the FDA, the word will be out in the next fifteen minutes.

So to play coy and not put it on one set of labels is just not going to work.

DR. ROMAN: I completely agree. The USA Today had the title, "Company wants date-rape drug approved for a sleep-disorder treatment." If that is in the newspapers--

DR. FALKOWSKI: This question is--it is my understanding, and I asked for clarification for this prior to the beginning of this meeting today--that we are voting here on specific questions. Is

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the determination of approval made upon FDA's consideration of what we talked about today?

DR. KATZ: Well, sure.

DR. FALKOWSKI: Is it made today?

DR. KATZ: Is the decision about what to do with the application made today? Absolutely not, no. Your opinions are all advisory. We take them very seriously and then we go back and we discuss it internally and we come to a decision, by the PDUFA due date.

DR. KAWAS: Going to the next question, can I ask, Dr. Katz--tell us what do you mean by certification and certification of physicians for prescribing?

DR. KATZ: There was some sense, internally, on the part of some people that physicians should--first of all, that it might be restricted to use only by sleep experts or

physicians would have to somehow take a test to show that they know about narcolepsy, that sort of thing, that they are appropriate prescribers in some sense.

DR. KAWAS: So we are not talking about the same thing that we were talking about previously, documenting that they have read

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whatever materials with the first prescription that they write?

DR. KATZ: It is something more than that.

DR. KAWAS: Okay. Let's take a straw vote on that. I think we can get past that one potentially fast, then. We are talking about more than just documenting that you have seen materials. Should certification of physicians, or some other restrictions, for prescribing Xyrem be required? Straw vote. How many people think yes? How many people think no? How many people are abstaining?

Let the record show that Dr. Wolinsky abstained. I am not sure, but I need to know why.

DR. WOLINSKY: Well, I am internally conflicted on this. When I say conflicted, I don't mean that I have some stockholdings anywhere but that I am--

DR. KAWAS: Anyone knows when they use that word they have time on the floor.

DR. WOLINSKY: I haven't come to a final decision in my own mind, but I would lean towards, I guess, certification of physicians when the circumstances are special. That doesn't actually keep patients from assessing care. It may mean that they have to be diagnosed in an appropriate

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situation and then can be cared for by a physician

who is willing to educate themselves about how to best use the drug.

I know that most of my colleagues won't like this but I think that this is where we have to go if medicine is to maintain credibility with an increasingly complex medical world that we live in.

DR. KAWAS: Now to go backwards to No. 5, which the questions deal with safe use by the patient. Should the patient sign an informed consent form before receiving the initial shipment of the drug? Straw vote. How many people think yes? How many people think no?

I won't ask Dr. Penn.

DR. PENN: I am worried about the medical-legal implications of informed consent in this situation. What does informed consent mean? Who signs it? All the things we get to in the controlled trials and that we deal with daily in the university setting.

It seems to me that, unless we work out the details, I can't feel comfortable voting for it.

DR. KAWAS: Actually, I abstained on the straw vote. My concern, and maybe my question is,

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informed consent about what? Presumably, we are talking about some version of the education that we have said they need to have. So is this just an acknowledgment of that education? What is it we want to make sure that they are informed about and get a signature to verify that?

DR. KATZ: Usually, informed consent is--it mostly emphasizes the potential risks. There are drugs, of course, that have informed consent as part of their approval. So that was the question.

Given the potential risks of this particular treatment, do people think that patients need to sign an informed consent.

It is unusual, but there certainly are precedents for it.

DR. PENIX: I think informed consent does imply a certain medical-legal situation but, perhaps, a contract like they use in many pain-management centers so that the patients acknowledge the problems with the dispensing of the drug and that type of thing. So maybe a contract would be a better idea than an informed consent.

DR. KATZ: Again, we put it on the list because it was raised internally at several discussions that we had. It doesn't mean that we

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necessarily, as a group, endorse it or most of us think it is a good idea. It was an option. We wanted to see what you thought about it.

DR. WOLINSKY: Call that question again.

DR. KAWAS: Does that mean you want to change your vote?

DR. WOLINSKY: I would like to withdraw my yes because this is much more complicated than immediately meets the eye and goes beyond what we really need, given all the other things that are already in this package.

DR. KAWAS: Okay. Do we need any more discussion before we call the question the second time? Any other comments people want to make? Should patients sign an informed-consent form before receiving the initial shipment of the drug. All who think yes, raise their hand.

[Show of hands.]

DR. KAWAS: Let's go around the table and identify the yes votes.

DR. SIMPSON: Simpson.

DR. FALKOWSKI: Falkowski.

DR. ROMAN: Roman.

DR. LACEY: Lacey.

DR. VAN BELLE: Van Belle.

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DR. KAWAS: All who think no.

DR. WOLINSKY: Wolinsky.

DR. KAWAS: Kawas.

DR. PENN: Penn.

DR. PENIX: Penix.

DR. KAWAS: Okay; we are set there.

Furthermore, should the patients be required to return a registry form before receiving the first shipment? Now, I assume that a registry form that we are talking about is kept by the sponsor?

DR. KATZ: Again, this analogous to what we talked about with the physician. The idea here was right now, the plan calls for such a form to be submitted after the first prescription is filled, that they have read the materials, they have received them and they have read them.

The question here was just whether or not you think that all has to happen before they even get the first dose.

DR. KAWAS: To my mind, that simplifies it considerably, then. Straw vote. How many people think yes, it should be done before not after or with the first dose.

DR. SIMPSON: Is this in addition to the

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consent form?

DR. KAWAS: This is different than the consent form; yes.

DR. SIMPSON: So, would it be in addition? I mean, if they did the consent form, would they need to fill out another form and send it in?

DR. KAWAS: I am not sure I am the right person to answer that because I don't know whether or not there is going to be a consent form. But maybe Dr. Katz could--

DR. KATZ: We asked it separately. They are two different things, although they are very closely related, I suppose. If you sign a informed consent that says, "I know what the risks are. "The card--what do we call it--a registry card. That presumably could be something that says, "I have read the material. I assert that I know how to draw the appropriate dose up. I know how to mix it. I know that I have to mix both doses first."

They have a sense of how it is supposed to be taken. So you would imagine it would have different information, could have different information, than an informed-consent form.

DR. KAWAS: So the registry, actually, has--it is not just a name, address, serial number

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of a person who is getting the drug. That is not what we are talking about in the registry form? We are talking about--

DR. KATZ: I think the idea here was, as I said before, whether or not, analogous to the question with regard to the physicians, that they have read the materials, what I intended, anyway, for this question was the exactly analogous situation for the patient.

Should the patient have to send the form

back. It would be a registry form, I suppose, in terms of who they are, but the pharmacist already knows who they are so they get into the registry that way, I suppose.

But whether or not they have read the material and they understand what the risks are and they understand how to take the appropriate dose, just before the first dose.

DR. KAWAS: Okay. Now I think we can better take a straw vote.

DR. SIMPSON: I just wanted to say I thought the consent form was that.

DR. KAWAS: But, having rephrased it for us, I think essentially what we are saying is now we have said that we want the physicians to certify

that they have read, know and understand some of the issues, the question is, should we ask the patients to do the same thing.

All who think yes, raise your hand.

[Show of hands.]

DR. KAWAS: And nos?

[Show of hands.]

DR. KAWAS: I think we have got a bunch of abstentions, mostly. Would you like to comment no your thinking?

DR. PENIX: I think it is just pretty complicated. I am not sure what a registry is going to do, what the drug company is going to do, with the information, who should keep the information. There are a lot of different issues, so I guess, in the late hour, I am going to abstain.

DR. LACEY: I would think these two things

could be combined into one some way or the other. If they can't, it is just getting to be too complicated in terms of all the forms and whatever, so they are losing interest in it.

DR. KAWAS: Are you talking about the patient or the committee? No; I think that something really important was just said here,

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actually. I think that if we put too many layers that nobody is going to pay attention to any single layer here. The whole idea is to do exactly the opposite, to have both the patients and the physicians taking this seriously.

Anybody can write in a patient's chart, "I have demonstrated how to do a safe dosage through the patient," and signed their initials. That only takes a few seconds. Getting them to spend the time to do it in the office is quite a different thing.

Obviously, what is more important is what is actually done and not what is certified. But let me see if I am getting the flavor from this committee that, in general, they think there should be one certification, registration, informed-consent process or whatever for both physician and for patient. Is that the gist of what we have been saying?

All who agree with that statement, straw vote, yes. All who think no.

DR. PENN: I abstain.

DR. KAWAS: Oh, gosh. And Dr. Penn abstains and we are not going to even bother finding out why.

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Dr. Katz?

DR. KATZ: Given the late hour and the list that still remains, I don't think we really need much in the way of discussion or even a vote, or a straw vote, on any of the other remaining issues.

I would ask, though, the committee members to just sort of quickly glance at it, or not, as you wish. But, again, if there is anything that strikes you as being a glaring omission in the program as proposed and as amended by your previous votes, just sing out. But I don't think we need any detailed discussion of the rest. I think we can sort of work it out.

DR. KAWAS: I would like to make the comment that, at least on the postmarket surveillance, I think there should be required postmarketing reporting, surveillance, monitoring.

DR. PENIX: In addition to the usual adverse effects, of course.

DR. KAWAS: Are there any other comments or thoughts from the committee particularly on the items we didn't specifically discuss like central pharmacy, postmarketing surveillance or other recommendations on protecting--

DR. SIMPSON: I guess there was just one issue brought up about who would police the policemen.

DR. KAWAS: You want to more specific in which policemen we are talking about?

DR. SIMPSON: The issue was whether the drug companies should be policing the correct usage of the drug and then, if that were the case, who would be policing that the drug company were doing it right. And, if the physicians are supposed to

be making sure that the patients are doing it right, and so on. That is what I mean. There is layer on layer here.

DR. KAWAS: Let's start with the first layer about if there is a surveillance or whatever from the company.

DR. KATZ: Again, in some sense, we are always in a position to oversee what the companies do in terms of meeting their appropriate reporting requirements and this sort of thing.

I think there is an understanding that what comes out of this registry and the experience will be reported to us. It will have to be reported to us. We will be working in close cooperation with the company to make sure that this

happens.

We won't be down at the first line making sure that the pharmacist is calling the patients within 24 hours. But, like many other things, there is an understanding that the company is responsible for making sure any given system of surveillance is working appropriately and we have interactions with them periodically.

So that is as far as we have gotten.

DR. LEIDERMAN: There are also precedents, at least for independent monitoring committees. And that has certainly been in approval agreements in the past. So that is the kind of thing that I think we need to work out.

DR. KAWAS: Unless there are any more burning comments or thoughts or theories, I would really like to thank the company, the agency, the members of the panel and all the invited speakers

as well as the speakers from the public forum for this interesting and challenging day

This meeting is now adjourned.

[Whereupon, at 6:00 p.m., the meeting was adjourned.]

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