

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE
OF THE
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:05 a.m.

Tuesday, April 24, 2001

Food and Drug Administration
ACS Conference Room, Room 1066
5630 Fishers Lane
Rockville, Maryland 20857

ATTENDEES

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ATTENDEES (Continued)

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C O N T E N T S

ISSUE: CLINICAL DEVELOPMENT OF PRODUCTS
FOR DROOLING IN NEUROLOGICALLY IMPAIRED CHILDREN

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P R O C E E D I N G S

(8:05 a.m.)

1
2
3 DR. CHESNEY: I'd like to welcome everybody
4 this morning to this session on clinical development of
5 products for drooling in neurologically impaired children.

6 I think we'd like to start with the introductions,
7 and why don't we start right here with Dr. Kelsey.

8 DR. KELSEY: My name is Jake Kelsey. I'm the
9 dental team leader in the Division of Dermatologic and
10 Dental Drug Products in the Center for Drugs at FDA.

11 DR. MATHIS: I'm Lisa Mathis. I'm a general
12 pediatrician in the Division of Dermatologic and Dental
13 Drug Products at CDER, FDA.

14 DR. RODVOLD: Keith Rodvold, Colleges of
15 Pharmacy and Medicine, University of Illinois at Chicago.

16 DR. FUCHS: Susan Fuchs, pediatric emergency
17 medicine, Children's Memorial Hospital, Chicago.

18 DR. DANFORD: Dave Danford, pediatric
19 cardiology, University of Nebraska Medical Center and
20 Creighton University Joint Division.

21 DR. EDWARDS: Kathy Edwards. I'm from the
22 Department of Pediatrics, Division of Infectious Disease at
23 Vanderbilt University in Nashville.

24 DR. GORMAN: Rich Gorman, general pediatrics,
25 Ellicott City, Maryland.

1 DR. SZEFLER: Stan Szefler, Department of
2 Pediatrics, University of Colorado in Denver.

3 DR. NELSON: Robert Nelson, critical care
4 medicine at the Children's Hospital, Philadelphia.

5 DR. O'FALLON: Judith O'Fallon, statistician at
6 the Cancer Center Statistics Unit, Mayo Clinic, Rochester,
7 Minnesota.

8 DR. FINK: Bob Fink, pediatric pulmonologist at
9 Children's National Medical Center here in Washington, D.C.

10 MS. PETERSON: I'm Jayne Peterson with the FDA.
11 I'm the Executive Secretary of the subcommittee.

12 DR. CHESNEY: Joan Chesney, the Infectious
13 Disease Division at the University of Tennessee in Memphis
14 and St. Jude's Children's Research Hospital.

15 DR. HUDAK: Mark Hudak, neonatology, University
16 of Florida, Jacksonville.

17 DR. KAUFFMAN: Ralph Kauffman, Children's Mercy
18 Hospital, Kansas City, Missouri, University of Missouri.

19 DR. SPIELBERG: Steven Spielberg, pediatric
20 drug development, Janssen Research Foundation, representing
21 PhRMA.

22 DR. WILFOND: Ben Wilfond, pediatric
23 pulmonologist at the Department of Clinical Bioethics at
24 the NIH.

25 DR. KODISH: Rick Kodish, Rainbow Center for

1 Pediatric Ethics, Rainbow Babies and Children's, Cleveland,
2 Ohio.

3 MS. WOERLY: Joni Woerly, State of Florida
4 Children's Medical Services, Jacksonville, Florida.

5 DR. GOLDSTEIN: Murray Goldstein, neurologist,
6 Medical Director, United Cerebral Palsy Research
7 Foundation.

8 DR. HAYS: I'm Ross Hays from the Departments
9 of Rehabilitation Medicine and Pediatrics at the University
10 of Washington and Children's Hospital in Seattle.

11 DR. PENA: I am Maria Pena from Children's
12 National Medical Center. I'm one of the pediatric ENTs
13 there.

14 DR. STIEFEL: Scott Stiefel. I'm a
15 pediatrician, adult and child psychiatrist at the
16 University of Utah, Department of Pediatrics and Child
17 Psychiatry, representing the American Academy of
18 Pediatrics, Committee on Children with Disabilities.

19 DR. CHESNEY: Thank you all very much.
20 Now Jayne Peterson is going to read the
21 conflict of interest statement.

22 MS. PETERSON: The following announcement
23 addresses the issue of conflict of interest with regard to
24 this meeting and is made a part of the record to preclude
25 even the appearance of such at this meeting.

1 Since the issues to be discussed by the
2 subcommittee at this meeting will not have a unique impact
3 on any particular firm or product, but rather may have
4 widespread implications with respect to an entire class of
5 products, in accordance with 18 U.S.C., section 208(b),
6 waivers have been granted to all members and consultants
7 who have reported interests in any pharmaceutical and
8 biologic companies.

9 A copy of these waiver statements may be
10 obtained by submitting a written request to the FDA's
11 Freedom of Information Office, room 12A-30 of the Parklawn
12 Building.

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

17 Dr. Ralph Kauffman would like to disclose that
18 he has contracts and/or grants from Bristol Myers Squibb
19 and he is a researcher for Bristol Myers Squibb, Janssen,
20 and Merck. In addition, he has received consulting fees
21 from Johnson & Johnson, McNeil Consumer Products, and
22 Purdue Pharma, and he is a scientific advisor to McNeil
23 Consumer Products and Purdue Pharma.

24 Dr. Steven Spielberg would like to disclose
25 that he is a full-time employee of Janssen Research

1 Foundation.

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

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

12 Thank you.

13 DR. CHESNEY: Thank you, Jayne.

14 For all the speakers, if you have a question,
15 please be sure to push the button down and turn the mike on
16 so the red ring is visible, and that allows your excellent
17 questions to be recorded for posterity.

18 Our issue this morning has to do with agents
19 that will reduce salivation and drooling, and the questions
20 specifically for the committee have to do with safety, dose
21 titration, and ethical issues. Dr. Dianne Murphy is going
22 to start our program with some introductory comments.

23 DR. MURPHY: I wanted to, once again, thank the
24 committee for their excellent discussion and questions
25 yesterday. You dealt with a chronic disease. I think the

1 word "insidious" was used. It develops over time and is
2 asymptomatic. It has an evolving epidemiology, has
3 therapies that had known toxicities, certainly had ethical
4 considerations in the questions that we asked you
5 yesterday.

6 Today we have some similarities and some
7 dissimilarities. It is a chronic problem. The efficacy is
8 not the question in this situation. We have a therapy that
9 we know is efficacious that we know is being used. It's
10 the dose. It's the ethics of how do we conduct a trial in
11 a population so we can determine the correct dose because
12 what is happening at the present at least -- you'll hear
13 more about this. What we are understanding the concern is
14 that the dose is being titrated individually for every
15 child in a population that may or may not be able to
16 communicate the discomfort and adverse effects of that
17 titration, dose-finding activity. Or a dose is given and
18 it's not effective, and then the child ends up on other
19 therapies or, as you will hear, other interventions that
20 may or may not have been the best if it turned out the
21 child was really being underdosed.

22 So, we have an issue that you will hear
23 discussed that we wish to contribute to the knowledge of
24 how to find an appropriate dose, but we think that there
25 are clearly ethical issues in how one would construct the

1 set of trials, and we seek your advice on whether we should
2 move forward in this arena, and if so, how.

3 Thank you very much.

4 DR. CHESNEY: Thank you for clarifying that,
5 Dianne. So, we're being particularly asked to address the
6 issue of how to construct trials for this population to
7 determine the correct dose.

8 Our first speaker will be Dr. Jake Kelsey who
9 is going to review the agenda and introduce us to the
10 issues.

11 DR. KELSEY: Thank you, Dr. Chesney.

12 On behalf of Dr. Jonathan Wilkin, who is the
13 Division Director for Derm and Dental, I'd like to thank
14 the subcommittee members, the presenters, and guests for
15 coming here today to help us address some of the issues
16 that impact on the development of drugs in this very
17 vulnerable patient population.

18 Drooling can be a problem in children with
19 cerebral palsy, as well as other neurodevelopmental
20 defects. There are currently no approved pharmacologic
21 therapies for drooling, though we are well aware that a
22 number of antimuscarinic drugs are used off label for this
23 purpose. As is often the case with off-label use, there
24 are limited studies in this particular indication. Safety
25 and dosing issues remain and formulations haven't been

1 developed for use in this population.

2 As we know from history, making new
3 formulations for children without well-controlled studies
4 can be dangerous. FDA would like to promote such studies,
5 hence this meeting in which we want to address special
6 considerations in studying drugs in this patient
7 population.

8 FDA would like the Pediatric Subcommittee to
9 address a number of issues. Assessment of adverse events
10 in this population is first. The appropriate formulations
11 for this use. How to develop useful dosing information for
12 this indication, and also unique ethical and legal
13 considerations that apply to studying this population. And
14 there are more detailed questions included in your meeting
15 package.

16 A number of people have inquired about why the
17 Division of Dermatologic and Dental Drug Products is the
18 group within the Center for Drugs at FDA that's charged
19 with looking at this issue. So, let me address that.

20 The dental team within Derm and Dental is
21 responsible for regulating products to treat xerostomia, or
22 dry mouth. The marketed products currently for xerostomia
23 are pilocarpine and cevimeline, and these are approved for
24 use in patients with Sjogren's syndrome and with
25 hyposalivation from radiation to the head and neck.

1 Because we're familiar with the physiology of
2 the salivary glands and the pharmacology of the muscarinic
3 agonists, it seemed reasonable for us to take a look at the
4 muscarinic antagonists as well. In addition, we're
5 fortunate in our division to have a pediatrician who has
6 treated patients with cerebral palsy and has used
7 glycopyrrolate, which is apparently the most frequently
8 used of these antimuscarinics. You'll hear from Dr. Lisa
9 Mathis in just a minute.

10 The agenda for the day is included in your
11 handout material. I'll begin by giving a brief review of
12 the neurophysiology of the autonomic nervous system and the
13 muscarinic receptors in particular. Dr. Mathis will then
14 discuss drooling in cerebral palsy patients, addressing the
15 extent of the problem, current treatment issues impacting
16 on conducting clinical trials. Her presentation will be
17 followed by an opportunity for questions and answers to the
18 two of us.

19 This will be followed by a presentation on
20 ethical issues in pediatric research by Dr. Benjamin
21 Wilfond from the NIH. He is a bioethicist and
22 pulmonologist.

23 He'll be followed by Dr. Maria Pena, an ENT
24 physician from Children's National Medical Center here in
25 Washington. She'll talk, from the clinical perspective,

1 | about the medical and surgical control of excessive
2 | drooling.

3 | Next will be Dr. Ross Hays from the University
4 | of Washington who is boarded in both pediatrics and
5 | physical medicine and rehabilitation, as well as having
6 | done a pain fellowship. He'll talk about methods for
7 | assessing adverse events in patients who have difficulty
8 | communicating.

9 | Following this group of speakers, there will be
10 | another opportunity for questions and answers.

11 | Finally, we'll hear from several advocates for
12 | patients with cerebral palsy. Dr. Scott Stiefel from the
13 | University of Utah is here representing the American
14 | Academy of Pediatrics' Committee on Children with
15 | Disabilities. He'll be followed by Dr. Murray Goldstein
16 | who is the Medical Director of the Cerebral Palsy Research
17 | and Education Foundation. The final speaker will be Ms.
18 | Belinda Hurlburt. She's the mother of a child, Ronny-Kay,
19 | who suffers from cerebral palsy. Both of them are here
20 | with us. Ms. Hurlburt will give her insight as someone who
21 | every day is involved in the issues that we're going to
22 | talk about. Again, there will be another opportunity for
23 | questions and answers.

24 | After a break, there will be an open public
25 | hearing period and again questions from the subcommittee.

1 I would also like to acknowledge one person who
2 won't be speaking today, Ms. Joni Woerly, who is from the
3 Florida State Department of Children's Medical Services.
4 As I say, she's not going to be speaking, but she's come
5 here today to offer her experience in treating patients
6 with cerebral palsy.

7 There are also a number of ethicists here today
8 who are included in your handout. I'd like to thank them
9 also for coming to help us with this issue.

10 As I said, our goal is to have pharmacologic
11 agents that can control drooling appropriately studied so
12 that they can be safely used in this patient population.
13 While we can't rule out the development of products with
14 novel mechanisms of action, those that are currently used
15 off label target the muscarinic receptors of the autonomic
16 nervous system that innervate the salivary glands.

17 The autonomic, or involuntary, nervous system
18 innervates the heart, blood vessels, visceral organs,
19 smooth muscles, and of interest today, the secretory
20 glands. The autonomic nervous system is divided into the
21 sympathetic and parasympathetic systems. Most target
22 organs are innervated by both sympathetic and
23 parasympathetic, and these two work in opposite ways to
24 create a balanced response, though in the case of salivary
25 glands, both the sympathetic and parasympathetic systems

1 stimulate secretion of saliva, though the sympathetic
2 stimulation is stronger.

3 In general, the neurotransmitter for
4 parasympathetic fibers is acetylcholine, and for
5 sympathetic fibers, norepinephrine. However, in the case
6 of the salivary glands, both sympathetic and
7 parasympathetic fibers employ acetylcholine as the
8 neurotransmitter. So, it's clear that any pharmacologic
9 mediation of drooling will have to target acetylcholine
10 receptors.

11 These are, in turn, divided into muscarinic and
12 nicotinic subtypes. The receptors in the salivary glands
13 are the muscarinic type. To refine things a bit more, the
14 muscarinic receptors in the salivary glands are the M3
15 subtype.

16 So, the salivary glands are stimulated by both
17 sympathetic and parasympathetic fibers with acetylcholine
18 as the neurotransmitter in both. The receptors are of the
19 muscarinic M3 type. To reduce salivation, we can employ an
20 antimuscarinic drug, and there are a number of
21 antimuscarinics already on the market for other
22 indications.

23 These drugs are effective in reducing saliva
24 secretion, and hence will be effective in decreasing
25 drooling. As will be discussed at some length, drooling

1 can be a significant problem in patients with cerebral
2 palsy and other neurodevelopmental defects causing
3 aspiration, maceration of the skin and the associated pain
4 that predispose to secondary infection, and can be a
5 barrier to educational opportunities and placement in these
6 patients.

7 However, many bodily functions other than the
8 salivary glands are mediated by cholinergic receptors.
9 Unfortunately, we can't be selective in blocking these
10 cholinergic effects. Blocking the cholinergic receptors
11 results in, among other things, dilatation of the pupils of
12 the eye causing blurred vision, increased heart rate
13 resulting in palpitations, decreased gut motility,
14 constipation, urinary retention which, of course, could be
15 painful and cause urinary tract infections. In addition,
16 the patients often experience reduced sweating and loss of
17 temperature control. These effects can be very unpleasant
18 for the patients, as well as, in some cases, dangerous.

19 Because the response to these agents varies
20 among patients and is dose-dependent, it's important to
21 have formulations that permit easy dose titration, and
22 clinical trials to support marketing of these products
23 should involve careful dose titration.

24 Also, because muscarinics are not selective and
25 because many patients with cerebral palsy and similar

1 diseases cannot effectively express their discomfort, it's
2 important that clinical studies involving these patients
3 maximize the possibility of identifying such responses for
4 safety reasons.

5 In summary then, the pharmacologic target for
6 controlling drooling is the muscarinic receptors, and we're
7 well aware that a number of antimuscarinic drugs are used
8 off label for this indication. However, because
9 antimuscarinics are not selective and extrasalivary
10 antimuscarinic effects can be dangerous and unpleasant for
11 the patient, we need studies to safely and properly dose
12 these products. And that brings us to the issue also of
13 the fact that dose ranging and assessment of adverse events
14 is problematic in this particular patient group. So, these
15 are the issues that we would like you to help us with
16 today.

17 Dr. Mathis will now go into more detail about
18 the problem of drooling in cerebral palsy patients, the
19 treatments, the need for marketed drugs, and the challenges
20 in studying drugs in this patient population.

21 Thank you.

22 DR. MATHIS: Hi. I'm Lisa Mathis, a general
23 pediatrician with the Division of Dermatologic and Dental
24 Drug Products.

25 Today we have several issues for the Pediatric

1 Subcommittee to consider.

2 The first is that drooling is a problem in
3 children with neurologic impairments, and I'll be
4 discussing drooling and the need to control drooling in
5 this patient population.

6 Also, I'll be discussing the need for studies
7 of medications and development of medications to control
8 drooling. As you know, currently there are no approved
9 pharmacologic therapies for this indication.

10 Then finally, we'll be discussing the
11 challenges of conducting these studies and the special
12 considerations that need to be given for studying drugs in
13 this patient population.

14 Drooling is a significant problem in children
15 with cerebral palsy and other neurologic impairments.
16 Although it's frequently referred to as sialorrhea in the
17 literature, it is not the result of hypersalivation.
18 Rather, it's impaired motor function that results in
19 difficulty swallowing.

20 The prevalence of cerebral palsy is 1.5 to 2.5
21 per 1,000 live births, and there are approximately 400,000
22 to 800,000 children and 400,000 adults in the United States
23 with cerebral palsy.

24 Of these patients, 25 to 35 percent have some
25 degree of drooling, and approximately 10 percent require

1 | intervention. There are also several other conditions
2 | associated with drooling in children, to include Down's
3 | syndrome, cerebral vascular accidents, hemiparesis, and
4 | degenerative diseases such as Rett's syndrome.

5 | The reason drooling requires intervention is
6 | that it may lead to aspiration. This can be life-
7 | threatening. It can lead to secondary pneumonias and is
8 | also associated with chronic pulmonary inflation. It can
9 | also lead to maceration of the skin. The large surface
10 | area that's involved in this breakdown can be very painful,
11 | similar to a burn. It also predisposes to secondary fungal
12 | and bacterial infections.

13 | Drooling may also compromise education, and it
14 | can do this by affecting attendance. It can affect the
15 | patient's ability to use electronic communication devices,
16 | and it can also actually take up all of the speech
17 | therapist's time. If a therapist is busy trying to work
18 | with a child to control drooling, they really don't have
19 | time to address other issues. It can also affect placement
20 | into special day-cares or special education programs, and
21 | this can have a profound effect not only on the child, but
22 | the child's family.

23 | There are several methods that are used to
24 | control drooling. The first is behavioral. And this is
25 | quite effective actually, but some patients have such

1 | severe involvement that the behavioral modifications just
2 | don't work. There's also pharmacologic, which we'll be
3 | discussing in great detail today. And there's surgical,
4 | and I'm sure Dr. Pena will be addressing this in a few
5 | moments. The surgery involves translocation and
6 | transection of the salivary ducts or neurectomies. It's
7 | irreversible. Everybody knows that there are a lot of
8 | risks associated with surgery, to include anesthesia,
9 | intubation, and in these patients who may have many
10 | surgeries over their lifetime, there's an increased risk
11 | for latex allergy.

12 | As mentioned by Dr. Kelsey, antimuscarinics are
13 | commonly used to inhibit salivation in these patients. The
14 | most commonly used medications include benztropine,
15 | glycopyrrolate, scopolamine, trihexyphenidyl, and several
16 | others.

17 | While there's a large body of experience in the
18 | pediatric practice using these medications for this
19 | indication, antimuscarinics are not approved for chronic
20 | use in children. They are approved for acute use in pre-
21 | anesthesia in children.

22 | Also, there are no commercially available
23 | pediatric formulations, and what this means is every time a
24 | parent goes to fill the prescription, individual
25 | pharmacists, using the IV solution or crushed tablets, mix

1 these with other ingredients to make a pediatric solution.
2 This can cause problems with dosing. It can cause problems
3 with stability and absorption.

4 Also, there's limited efficacy, safety, and
5 dosing information from clinical studies.

6 The reason why dosing is so important in these
7 medications is because of the known adverse event profile.
8 Antimuscarinic effects on the neurologic system include
9 headache, irritability, nervousness, confusion,
10 disorientation, and depression. Special senses can be
11 involved with blurred vision and loss of taste.

12 The gastrointestinal system can be involved
13 with nausea, vomiting, paralytic ileus, and constipation,
14 and we can see tachycardia and palpitations in the
15 cardiovascular system.

16 Antimuscarinic effects on the urogenital system
17 include urinary retention and dysuria, and there are
18 several others, to include hyperthermia, due to inability
19 to sweat, and xerostomia. It should be noted that
20 xerostomia is actually the effect that we're looking for
21 here, but not absolute xerostomia. Dry mouth is not only
22 very uncomfortable, but it can lead to oral abrasions and
23 an increase in dental caries.

24 Clinical trials are necessary to evaluate new
25 formulations. Commercially available formulations would

1 increase safety and consistency in administration, and
2 developing appropriate concentrations would allow
3 caregivers to titrate the dose in small increments.

4 Clinical studies are also necessary to
5 determine pediatric dosing. We know, in indications other
6 than in drooling, the optimal dose must be individualized.
7 The response is variable from patient to patient. In the
8 studies that we do have on children with drooling, we know
9 that the degree of drooling at baseline is a poor predictor
10 of response to these medications. Small dose adjustments
11 must be made until the benefit is achieved or side effects
12 occur.

13 If we look at the dose-response curve of
14 atropine, which is the prototypic drug for all of the
15 antimuscarinics, you can see that with small increases in
16 dose, you have a large increase in side effects. Looking
17 at the effects of atropine in relation to dose, we can see
18 that at .5 milligrams, there's slight cardiac slowing, some
19 dryness of the mouth, and inhibition of sweating. At 1
20 milligram, you see tachycardia, definite dryness of the
21 mouth, and dilatation of the pupils. At 2 milligrams,
22 there's tachycardia, palpitations, marked dryness of the
23 mouth, and blurring of near vision, and at 5 milligrams,
24 all of the above symptoms become marked, adding
25 restlessness, fatigue, headache, decreased urination, and

1 reduced intestinal peristalsis.

2 It's important to note that some patients might
3 have adverse events that would prohibit them from using
4 this medication before they achieve any benefit, while
5 others can go up to the highest doses, achieving benefit
6 without experiencing any side effects.

7 While we know that clinical trials are
8 necessary, there are also great challenges of conducting
9 clinical trials in children with special needs. These
10 challenges include patient selection, consent, which
11 children cannot give, assent, and communication. Then
12 there are also challenges to evaluating efficacy and safety
13 in this population.

14 In assessing efficacy, it's important to
15 determine what dose provides the appropriate balance
16 between control of drooling and adverse events. As we said
17 earlier, the efficacy of these products is known. It's
18 very good. But absolute xerostomia is not in the best
19 interest of the patient.

20 Also, drooling can vary from hour to hour, and
21 the assessments of efficacy must be done multiple times
22 during the day.

23 What objective tools can be used to measure
24 efficacy? The Teacher's Drooling Scale has been used in
25 the past and is actually referenced in some of the papers

1 that are in your packet for your information.

2 But then we have to discuss who would
3 administer the tools. Will it be the caregiver who best
4 knows the patient? Will it be the teacher who is with the
5 patient during the day while the medicine is having most of
6 its effect? Or will it be study personnel who may be
7 considered more objective, or a combination of all of the
8 three? Given this, you see that the tool that is going to
9 be used has to be practical to be used multiple times
10 during the day, and it also has to address the fact that
11 there's a need to minimize interrater variability.

12 Assessing safety has some of the same problems.
13 Assessment of pain and discomfort can be very difficult in
14 this target population. In most clinical trials, self-
15 reporting of pain and discomfort is considered the gold
16 standard. However, patients with cognitive disability or
17 inability to communicate cannot self-report, and failure to
18 recognize side effects could lead to patient suffering and
19 long-term morbidity.

20 Because we know that adverse events can be
21 serious, it's very important for us to try to figure out
22 what kind of tools can be used. Some pain scales have been
23 developed in the past for use in noncommunicative children,
24 and they're basically checklists of behavioral and/or
25 physiologic characteristics, and any change from baseline

1 is a signal that the patient is either uncomfortable or in
2 pain. However, that signal is very nonspecific. It's hard
3 to determine exactly what's bothering the patient.

4 Again, we have to ask who will administer the
5 tool. Will it be the parent who best knows the patient and
6 is an invaluable resource in determining whether or not the
7 child is uncomfortable? Will it be the teacher who may be
8 with the child while the medication is having its most
9 effect? Or will it be study personnel or a combination of
10 all of the above?

11 We've covered a lot of ground in this talk, and
12 all of these subjects will be covered in more detail in a
13 few moments by our speakers.

14 In conclusion, I'd like to say that drooling
15 can be a serious problem in children with neurologic
16 impairments.

17 Pharmacologic control appears to be effective
18 for some patients.

19 There is a need for well-designed studies to
20 provide information on dose-related safety and efficacy.

21 Studies must be conducted in a manner that
22 respects the rights of the patients and results in
23 beneficial clinical information.

24 At this time, Dr. Kelsey and I will take
25 questions from the subcommittee to clarify our

1 presentations.

2 DR. CHESNEY: Dr. Szeffler.

3 DR. SZEFLER: Is there a time-of-day phenomenon
4 that goes in terms of dosing? It sounds like this field is
5 not well researched, and I guess as a panel we might be
6 instructed in terms of some of the principles. Is there
7 greater secretion nighttime versus daytime? Is there
8 something different that might be considered in terms of
9 dosing principles like chronopharmacology?

10 DR. MATHIS: Dr. Pena might actually be able to
11 help you with the variation of drooling during the day. I
12 imagine that during the daytime, when the child is upright,
13 you're probably going to notice a lot more anterior
14 drooling. However, posterior drooling goes on as well,
15 which is what results in aspiration.

16 At least some of the medications seem to have
17 their greatest efficacy approximately 2 hours after
18 administration, but all of the agents differ.

19 DR. CHESNEY: Dr. Goldstein.

20 DR. GOLDSTEIN: As a partial response to your
21 question, I think we've got to continue to remember that
22 salivation is not the problem. The problem is
23 fundamentally coordination of tongue and swallowing reflex.
24 Even though we're looking at one approach to solving the
25 clinical issue, we are not approaching the pathological

1 | issue at all by this approach. So, one has to be extremely
2 | careful that we realize that we're proposing to address
3 | symptoms rather than the basic pathology which raises other
4 | kinds of issues about whether there are pharmacologic
5 | approaches to addressing the basic pathological entity.

6 | DR. CHESNEY: I have a couple of questions. I
7 | thought that was a very interesting question which raised
8 | two thoughts. One is, is there in fact increased
9 | salivation at the time of eating, and is it fair to say
10 | that most of these children will not be eating by mouth?
11 | Or they could be eating, as well as having a gastrostomy?
12 | If there's difficulty in swallowing, is it enough that they
13 | can't eat, and do you see increased salivation at the time
14 | of feeding?

15 | DR. MATHIS: I'm not sure about increased
16 | salivation at the time of feeding, although I would imagine
17 | as a reflex that that would indeed occur.

18 | Many of these children actually take food
19 | orally, as well as gastrostomy tubes. But many of the
20 | patients are able to swallow food, and frequently these
21 | patients, if they have behavioral therapy and they remember
22 | to constantly swallow, they can actually swallow their
23 | saliva as well. So, while they're eating and they're able
24 | to think about the process of swallowing, they can do that.
25 | It's just that throughout the day, they would constantly be

1 | having to remember to swallow, just like having to remember
2 | to breathe. So, many of them do eat.

3 | DR. CHESNEY: Are there consistent things that
4 | can be done at night, in other words, like we do for
5 | reflux, that they don't lie flat, they lie upright. You
6 | mentioned aspiration is more likely when they're, I assume,
7 | lying flat at night. Is that pretty routine to have these
8 | children sleep in a more upright position, or are there any
9 | mechanical things? Maybe we're going to be hearing more
10 | about that, but are there things that can be done at night
11 | other than medication?

12 | DR. MATHIS: It would seem logical to me that
13 | there are. However, I'd defer this question to the
14 | pulmonologists or other people who may be able to address
15 | this.

16 | DR. CHESNEY: Dr. Fink.

17 | DR. FINK: There are things that you can do at
18 | night just in terms of side position or even going to a
19 | prone sleeping. But it leads to problems with maceration
20 | because unless you continually change the padding, the kids
21 | drool all night long.

22 | My other comment was I think in the
23 | presentation we shouldn't underestimate the significance of
24 | this problem, because it's not just cerebral palsy. There
25 | is a large group of severely retarded pediatric patients

1 from all sorts of various brain injuries that this is a
2 chronic, severe problem in also in terms of their
3 management.

4 DR. CHESNEY: I have another question. This
5 issue of the reaction to these drugs being such an
6 individual phenomenon. I was impressed that you said some
7 will have side effects before they have any effect on
8 salivation and vice versa. So, it seems that ultimately
9 any study is going to have to focus on the individual
10 child's response. Is that a fair statement?

11 DR. MATHIS: Yes, that is. Ultimately what we
12 would like to see happen are the tools for assessing both
13 safety and efficacy validated and incorporated into
14 labeling so that the caregivers could make fine tuning of
15 the dose to control the drooling balanced against the
16 adverse event, somewhat similar to a patient with diabetes
17 doses their insulin.

18 DR. CHESNEY: So, that would be the ultimate
19 goal in the labeling, to point out that this is a very
20 individual phenomenon.

21 DR. MATHIS: Right.

22 DR. CHESNEY: Thank you for clarifying that for
23 me.

24 Yes.

25 DR. KODISH: A GI question, if someone can

1 answer for me. I know we'll hear more about the surgical
2 solution later, but it seems like the complete cutoff of
3 salivation and over-medicating to do a pharmacologic cutoff
4 of salivation. Aside from the oral implications of that,
5 are there not lower GI but esophageal, gastric, digestive
6 function problems that would come from that? Does anybody
7 know?

8 DR. FINK: I can comment on it. Constipation
9 is already a major chronic issue in most of these patients,
10 and typically the most clinically significant side effect
11 is constipation, although there are stool softeners,
12 Fibercon. There are lots of ways to deal with the
13 constipation. That's a very obvious symptom usually.

14 The urinary retention is probably more
15 bothersome because I think frequency of urinary tract
16 infections again is frequent in this population, but
17 something that isn't clinically evident. So, if I put a
18 patient on one of these medicines and increase of frequency
19 of their urinary tract problems, I am much less likely to
20 have that reported to me than constipation.

21 DR. KODISH: But are there going to be
22 worsening nutritional issues, or would that not be a
23 problem here?

24 DR. PENA: From a surgical standpoint, I
25 haven't encountered any problems with worsening nutrition.

1 DR. CHESNEY: Dr. Spielberg.

2 DR. SPIELBERG: I need some help, having
3 forgotten some autonomic pharmacology. Anything different
4 that can lead to new drug development with respect to
5 cholinergic receptors in salivary glands versus elsewhere,
6 other than trying to keep things out of CNS, such as
7 scopolamine and things that are going to have more profound
8 CNS effects?

9 And secondly, what about afferent loops that
10 lead to salivation? The efferent is obviously
11 acetylcholine, but the afferent loops that, for example,
12 when you put lemon juice in the mouth that lead to
13 salivation -- do we know what transmitters are involved in
14 mediating those afferent loops that increase salivation?
15 And are those potential targets?

16 DR. KELSEY: I don't know that I can answer
17 your question, Dr. Spielberg, other than to say that from
18 what I've seen in the literature, no one is using this. It
19 hasn't been tried. So, other than that, I really can't
20 tell you.

21 DR. CHESNEY: Yes, Dr. Walters.

22 DR. WALTERS: About a third of the children
23 with cerebral palsy seem to have intact cognitive function.
24 I wanted to ask are there any differences between children
25 with intact cognitive function and those who have

1 intellectual disabilities in terms of their ability to
2 respond to behavioral interventions or even the magnitude
3 of the problem of drooling?

4 DR. MATHIS: There actually are differences.
5 Patients with cognitive disability can't really be taught
6 to constantly be swallowing. I imagine Dr. Goldstein is
7 going to cover this in more detail in a few moments.

8 But there are also children with very good
9 cognitive ability who do not have the motor function to be
10 able to swallow. Even though they can be taught and they
11 can constantly be thinking about it, they still can't
12 coordinate the swallow.

13 So, there is a difference, but it goes both
14 ways in both segments.

15 DR. CHESNEY: I was intrigued by Dr. Kodish's
16 question. What is the total volume of saliva that's made
17 over a 24-hour period? Do we know, roughly? Because I
18 think your question had to do with whether, say, you put
19 out a liter and you have a liter less in the GI tract, what
20 does that mean. Yes, Dr. Stiefel.

21 DR. KODISH: In titration, essentially we're
22 titrating that volume.

23 DR. STIEFEL: I can somewhat address that from
24 the literature. Most of the original physiology was done
25 back in the 1940s and 1950s. It's somewhere between a half

1 and 1.5 liters. So, it's extraordinarily variable in
2 regards to that.

3 Things even such as concentration can affect
4 the amount of salivary volume. Actually the responses are
5 different in cerebral palsy versus someone with mental
6 retardation. In mental retardation, concentration
7 increases salivary production. So, it's a very complex
8 issue and there's extraordinary variability.

9 DR. CHESNEY: Do you know the answer to the
10 question of -- or maybe Dr. Pena does. We're getting ahead
11 of ourselves, but since we're on the issue. Does it affect
12 the GI tract if you cut off salivation, period?

13 DR. PENA: No. Generally with surgical
14 procedures, you can't get rid of all salivation. The
15 majority of the procedures either involve four duct
16 ligation of the parotid Stensen's ducts and Wharton's ducts
17 or excision of the submandibular glands with tying off the
18 parotid ducts. You're still going to have 40 to 50 percent
19 produce just by the minor salivary glands in the palate,
20 the oropharynx. You cannot get rid of that. The
21 submandibular glands produce anywhere between 30 to 70
22 percent of the saliva, and parotid being 10-15 percent.
23 So, you're never going to get rid of all the saliva.

24 DR. CHESNEY: Thank you. Sorry for stealing
25 your thunder.

1 Dr. Fink.

2 DR. FINK: Actually I think we do know the
3 answer to your question directly, which is that 20 years
4 ago, 30 years ago, in the days when the standard treatment
5 of tracheoesophageal fistula was a spit fistula and leaving
6 the blind pouch, those children were totally disconnected
7 from their GI tract for periods of 3 to 4 years with no
8 salivary or tracheal secretions reaching the GI tract, and
9 they did just fine with tube feedings. So, mother nature
10 may have given us the answer to that one.

11 DR. CHESNEY: Thank you.

12 Dr. Kauffman.

13 DR. KAUFFMAN: What's known about receptor
14 selectivity of any of the antimuscarinics? Are they all
15 nonselective antagonists, or are some of them more
16 selective for the M3 than others?

17 DR. KELSEY: Yes, some are. I can't give you
18 the list, but I know, for example, atropine is not
19 particularly selective for M3, whereas glycopyrrolate is.
20 The advantage with glycopyrrolate is that it doesn't cross
21 the blood-brain barrier to any significant extent. So,
22 that's one of the reasons that it's used. But there is
23 some selectivity as far as the antimuscarinics that are
24 available.

25 DR. KAUFFMAN: And a related question. What's

1 | known about how feasible it actually is to give enough
2 | glycopyrrolate to reduce salivation satisfactorily without
3 | producing the dose-related side effects? It looks to me,
4 | from what little I know about autonomic pharmacology,
5 | they're so tightly tied together, that you have a very,
6 | very narrow therapeutic window here.

7 | DR. KELSEY: Well, it's true that there is a
8 | rather steep dose-response curve. One of the slides that
9 | Dr. Mathis showed addressed atropine, but it showed the
10 | various doses and the responses that could be expected.
11 | Unfortunately I guess for this particular question,
12 | salivation tends to be reduced by lower levels of
13 | antimuscarinics than the levels that cause reduction in gut
14 | motility, urinary retention, and so forth, but it's quite
15 | variable, and again the response is very steep.

16 | When we get into talking about formulations,
17 | one of the things that we would expect to hear is that the
18 | concentrations of the solutions should be such that you can
19 | give very small doses in a reasonable volume of solution in
20 | order to address these kind of problems. We also would
21 | like to hear what people think about tools for assessing
22 | the adverse events in this population so that we can
23 | carefully titrate and how we can help the caregivers to
24 | titrate these doses.

25 | DR. CHESNEY: Dr. Szeffler.

1 DR. SZÉFLER: Just one quick question. In the
2 pulmonary world, drugs are being developed to separate out
3 muscarinic properties. I don't know if you're aware or if
4 even the pharmaceutical firms have thought of it, but some
5 of these drugs that are being screened, I'm not sure in
6 terms of their pulmonary effect and their effect on
7 salivary mechanisms play a role. But you might keep an eye
8 on those drugs. They're usually developed for the inhaled
9 route, but they may have applications.

10 DR. CHESNEY: Thank you for addressing our
11 questions.

12 Dr. Wilfond is going to talk to us about some
13 of the ethical issues involved in titrating these
14 medications in patients who can't always tell us whether
15 they're in pain or suffering side effects.

16 DR. WILFOND: Thank you. It's a pleasure to be
17 here. As a pulmonologist, most of the children I see with
18 swallowing dysfunction are there because of problems of
19 aspiration. So, for me this was a pretty obvious issue and
20 it would be nice to have more data about this. So, I come
21 with that bias.

22 The Federal regulations for human subject
23 research have a number of criteria to assess whether a
24 particular research study is ethical. On the slide in
25 front of you, I listed the six main criteria. What I'll be

1 | doing is focusing on the two that are highlighted in
2 | yellow: the issue of how to balance risk with benefit and
3 | issues related to subject selection.

4 | Additionally the pediatric regulations
5 | categorize research based upon the risks and benefits. I
6 | just wanted to point out that these types of studies would
7 | be studies that would be in the upper row of offering a
8 | prospect of direct benefit, so that we would be asking
9 | questions about whether the risks are justified by the
10 | benefits and whether that balance is favorable as the
11 | alternative, which in this case would be the lack of
12 | clinical trials.

13 | So, when I spoke with Dr. Mathis a month ago, I
14 | said, what are the issues? Because to me, I have to admit,
15 | I initially struggled to think of what they were. She gave
16 | me some thoughts about what the issues were, which I will
17 | try to address today.

18 | The first had to do with who decides whether
19 | drooling is severe enough to warrant a study enrollment,
20 | and might parents want intervention for their convenience
21 | rather than for the best interest of the child.

22 | The second issue is, how can side effects be
23 | assessed in children with limited ability to communicate?
24 | So, is it possible that children would be harmed without
25 | realizing it? And might parents minimize side effects to

1 | continue the trial or just because they're unaware that
2 | there's a side effect going on?

3 | The last issue was the equity issue. Was it
4 | appropriate to enroll children who are not in the custody
5 | of their parents? On one hand, would it be wrong to
6 | exclude them because they would be denied access to an
7 | important intervention, or would it be wrong to include
8 | them because it might take advantage of particularly
9 | vulnerable children?

10 | So, let me give you my very quick answer to
11 | those questions, and then I'll try to give you a little
12 | more detailed answers.

13 | With regards to the issue of whether or not
14 | this is being done for the convenience of the parents, I
15 | think it's important to point out, whether it's true or not
16 | true, which I'll get to in a moment, that that's an
17 | objection not about the research itself, but about the
18 | actual intervention. So, even if the intervention was
19 | effective clinically, that would be an objection that would
20 | be raised not by the research, but by whether it's
21 | appropriate to use this medication. As I'll describe in a
22 | moment, I don't think that's an issue.

23 | A second point is, again, the benefits and
24 | harms of being in such a study are certainly as favorable
25 | as the alternative of using these drugs in an unstudied

1 | situation where we don't have the information about the
2 | proper dose.

3 | The last point I'll make is that while there
4 | may not be a compelling reason to exclude people who are
5 | not in the custody of their parents from such trials, it
6 | wouldn't be a good idea to actively go out of your way to
7 | try to recruit such subjects as well.

8 | To try to flesh it out a little bit more, let
9 | me go to the next slide. Pediatric care decisions are
10 | often made not exclusively just for the best interests of
11 | the child, and it's very common to include parental
12 | convenience and reassurance in much of pediatric care. I
13 | think as a parent we're all familiar with that practice.
14 | We also realize that short-term interests and long-term
15 | interests are very complicated.

16 | Before I get to the medical issues, I was
17 | talking with Rick Kodish earlier this morning, and we were
18 | discussing the fact that when a family decides to move to a
19 | different geographic location, it usually causes lots of
20 | disruption for the child. It's not usually for the
21 | immediate best interest of the child, but yet parents do
22 | it. Often the hope is that in the long term it will be a
23 | good thing.

24 | To use a more clinical example, metoclopramide
25 | for reflux. While it may be used to decrease aspiration or

1 apnea, in less severe cases it's used because kids are
2 puking a lot, and it is unpleasant to wash clothes very
3 often. But I don't think we give much thought to whether
4 that's an inappropriate thing to treat reflux in spite of
5 the potential risks.

6 Again, as a pulmonologist, we use apnea
7 monitors for reflux associated apnea. There's no evidence
8 to suggest that the apnea monitors actually prevent any
9 serious life-threatening events. They're really primarily
10 used for reassurance. In fact, if we actually thought a
11 child was having serious life-threatening events, we
12 wouldn't send them home. We'd be trying to come up with a
13 better solution to that problem. So, again, this is
14 another example of providing intervention for reassurance,
15 even though it might cause some risk as well.

16 My favorite one is diapers. This is purely for
17 convenience of care. Infants do not need diapers, but it
18 would be incredibly challenging to take care of infants
19 without those diapers. I'm saying that sort of jokingly,
20 but actually quite seriously in the sense that it troubles
21 me in some ways that we look at children with disabilities
22 in a different way and aren't willing to acknowledge that
23 the caregivers have needs as well too, as we think about
24 how to balance the needs of the caregiver and the child,
25 and realize that ultimately, just as having diapers allows

1 a parent to take better care of their child overall, I
2 think these medications can have the same beneficial impact
3 on children as well.

4 So, the other objection is there might be
5 limitations to parental assessments. One is their ability
6 to make an assessment about the severity of benefits or
7 harms. Certainly it's routine to rely on parents to make
8 observations about infants, even though we also know that
9 well-meaning parents may not always provide accurate
10 historical information. And we often will use objective
11 assessments to sort this out, whether it's weighing a
12 patient to assess dehydration, using a Ph probe for reflux,
13 looking at apnea monitor downloads for children who are on
14 monitors, or even with children with swallowing
15 dysfunction, looking for evidence of aspiration to get some
16 sense of the severity. So, I think the notion of trying to
17 use objective tools as a component to any sort of a study
18 is an appropriate thing, and I would certainly support
19 that.

20 With regards to willingness, again most parents
21 make very reasonable decisions with regards to their
22 children, but we also know that some parents make very bad
23 decisions, as evidenced by all the cases of child abuse
24 that we see in the country. But there is no reason to
25 assume that a person who is a caregiver but is not the

1 parent, such as a foster parent, is any more likely to harm
2 their child than regular parents do. So, I think that from
3 the point of view of the question of whether or not it's
4 appropriate to include children who are not always in the
5 custody of their parents, from an ethical point of view,
6 there's no reason to assume that those children will be
7 treated any differently.

8 The second major point I wanted to make is the
9 fact that because these drugs are being used without the
10 benefits of trials, they're being exposed to harms without
11 clear evidence of exactly how the benefits will play out.
12 Given this lack of evidence, there would be sufficient
13 equipoise to conduct a trial. Actually I said placebo-
14 controlled trial, but I realize from the discussion that it
15 sounds like the issue is really more of dose titration than
16 just whether it works or not. So, that's probably not a
17 correct thing to say there.

18 The last thing I wanted to point out was the
19 issue of what to do for children who are not in the custody
20 of their parents. Because this trial would be approved
21 with the prospect of direct benefit, within the regulations
22 themselves, there's no specific prohibitions about having
23 children enrolled who are not in the care of their parents.
24 There are specific provisions for wards of the state for
25 research where there's no prospect of direct benefit and

1 | more than minimal risk. But in this case that would not
2 | apply.

3 | Nevertheless, there's the question of should
4 | IRBs limit enrollment to children living with their
5 | parents. Again as I said, it probably is reasonable to try
6 | to avoid recruiting from more vulnerable settings, such as
7 | residential settings. It's worth noting these children
8 | would have access to these medications off trial. But in
9 | fact, most children who have swallowing dysfunction, for
10 | whatever reason, generally do live with their parents. I'm
11 | saying that not as an empirical fact from knowledge of the
12 | entire population, but just from my own experience as a
13 | clinician. The vast majority of children I see are home
14 | with their parents.

15 | The last thing is that the scientific
16 | objectives of such a study could be met without enrolling
17 | children who do not live with their parents. So, there
18 | would be no need to do that if you didn't want to.

19 | So, in conclusion, I think that the clinical
20 | complications of drooling are similar to those routinely
21 | addressed in children by medical and surgical
22 | interventions.

23 | The challenges of assessing risk and benefit
24 | would be inherent in any trial of young children. Any
25 | trial with infants would raise the same questions of these

1 assessments.

2 There's no reason to be more critical of
3 parents of children with disabilities in making enrollment
4 decisions or assessments than for other pediatric trials.

5 With that, I'll end.

6 DR. CHESNEY: Thank you very much.

7 Our next speaker is Dr. Maria Pena who is going
8 to talk to us about the medical and surgical management of
9 drooling.

10 DR. PENA: Good morning and thank you for
11 allowing me to present my data.

12 When I talked to Dr. Mathis, what I've done --
13 I have an oromotor dysfunction clinic in Children's. What
14 you're going to hear is an anecdotal experience that's been
15 going on for about two years at Children's both in terms of
16 the glycopyrrolate and surgical management.

17 I'm going to pass out what we're currently
18 using to assess saliva management in patients, the initial
19 interview. This comes from the Melbourne Group, the Saliva
20 Control Group in Melbourne, Australia, as well as a rating
21 scale chart for the parents and school people taking care
22 of these children to assess how well we're doing in terms
23 of the glycopyrrolate. As of yet, I don't have a
24 compilation of the data. We're in the process of
25 collecting it.

1 As we all know, drooling basically is the
2 abnormal spilling of saliva from the mouth onto the lips,
3 chin, the neck, and the clothing.

4 What we've done at Children's is basically
5 develop an interdisciplinary approach. We have a team that
6 consists of a speech and language pathologist, physical
7 medicine and rehabilitation, and myself, an
8 otolaryngologist. At times we have a pediatric dentist
9 that participates with us. Then we evaluate these
10 children.

11 That's essentially what I've just told you.

12 Basically management of these children can be
13 divided into correcting situational factors and oromotor
14 exercises. I'm not really going to talk about those,
15 although they are addressed in the team meetings with the
16 speech and language pathologist. In the packets that are
17 being passed out, you have recommendations from the speech
18 and language pathologists for some of the oromotor
19 exercises that caregivers can participate in along with the
20 children. The talk is basically going to be directed
21 toward medication and a little bit of surgery.

22 In terms of the glycopyrrolate, as we all know,
23 it doesn't cross the blood-brain barrier. 95 percent
24 efficacy. That's true essentially in the 25 children that
25 I've followed, although the reports in the literature claim

1 that there's a lot less. And I'm going to address oral
2 administration.

3 In our clinic, we've followed approximately 25
4 patients that we've evaluated over 2 years. Essentially we
5 meet one afternoon a month. The patients are referred to
6 us from pediatric specialists, from pulmonologists, other
7 otolaryngologists, and GI.

8 Our patient profile. Basically our children
9 have cerebral palsy, mental and developmental delays, and
10 craniofacial syndromes.

11 The initial visit entails a comprehensive H&P
12 from all three specialists. Basically we all come in the
13 room at the same time and do a detailed evaluation. We
14 also have the saliva control assessment, which we review at
15 the end of the day because of the time limits, to get
16 another feel for actual parent and the patient and the
17 caregivers, if you would.

18 We're treating 14 patients currently with
19 glycopyrrolate.

20 This is just to remind me when we initiate
21 glycopyrrolate side effects, we go through a list of the
22 complications, essentially dry mouth, thickened secretions,
23 and flushing.

24 The urinary retention, constipation, and drug
25 interaction. Drug interaction is an important one because

1 a lot of these patients are on seizure medications,
2 Depacote in particular, which we have to monitor levels
3 because it does interact with the Robinul.

4 As you know, glycopyrrolate is available in
5 chewable tablets and liquid, and it's the injectable IV
6 solution that we're using. Because of the children's
7 limitations, generally that's what works best for the
8 children in terms of what form we administer it.

9 The IV dose, as you know, is given three to
10 four times a day. With the oral dose, we're dosing
11 anywhere between three to four times a day.

12 The ranges that we're using for the oral IV is
13 anywhere between .04 milligram per kilogram per dose to .1
14 milligram per kilogram per dose. We're generally starting
15 off with actually twice a day. Then what we have the
16 parents and the school do is call back within a month and
17 tell us how effective is that is. Then we increase it to
18 three times a day and then go up a half a milligram per
19 kilogram. We seem to be having some success with that.

20 Then just for the sake of completeness, the
21 oral dose or the IV is 10 times what you would give
22 parenterally. These are the recommendations for parenteral
23 dosing, .004 milligram per dose to .01 milligram per dose.
24 And remember this is Q3 to 4 hours.

25 So, how do we follow up the patients? This is

1 | presuming we've started them on glycopyrrolate, of course.
2 | Then we see them every 3 to 6 months, as well as the phone
3 | calls that we get from the caregivers and the school to see
4 | how they're doing in terms of the glycopyrrolate dose that
5 | we initiated. In your packets, there's a rating scale
6 | chart which we have the caregivers and the school fill out,
7 | two of the charts per week, if at all possible.

8 | That's what I just told you. I try to have the
9 | school and the caregiver -- it allows us to pick up to see
10 | if things are really consistent in terms of the drooling.
11 | Like I said, two charts per week.

12 | What am I looking for? I'm looking for
13 | severity and frequency of drooling and also what are the
14 | children doing when they're drooling the most.

15 | The severity is pretty straightforward, just
16 | how many secretions are around the child. Is the child
17 | dry? Is there a mild amount, moderate amount, and severe
18 | and profuse?

19 | The next slide has to do with the frequency.
20 | Are they drooling at all? Is it minimal? Is it
21 | occasional? Frequent and profuse and constant. Most of
22 | the patients that we deal with basically fall in this
23 | category between 4 and 6 pre-glycopyrrolate.

24 | Of the patients we've treated, we've had
25 | actually three what I would call significant complications.

1 The first one is constipation. That child
2 needed multiple disimpactions. What actually had happened
3 is that the parent was unaware. Well, I shouldn't say she
4 was unaware, but she didn't put 2 and 2 together that the
5 constipation was getting worse because of the
6 glycopyrrolate. The child understands. So, she really
7 likes the Robinul. It really helps her socialize. I
8 didn't find out about this until the second emergency room
9 visit. We've titrated down the dose of the glycopyrrolate.
10 I have to hear back from them. You're going to meet them
11 this afternoon and they'll tell you their personal
12 experience with glycopyrrolate and what happened.

13 The second child, thickened secretions. It's
14 especially relevant because a lot of the patients I treat
15 also have tracheotomies and that can become a potential
16 life-threatening problem. This young lady developed much
17 more mucus plugging. The caregiver, the nurse, was
18 actually very savvy and realized what was going on because
19 she was having to do multiple trach changes as opposed to
20 the one a week that we require. We titrated down her
21 glycopyrrolate and she seems to be doing better.

22 Then the last one has to do with the drug
23 interactions and Depacote in particular. This young lady
24 was doing quite well with the Robinul, but I check the
25 Depacote levels once a week because we know it can

1 | interfere with the metabolism. She was having difficulty
2 | with the Depacote level. Actually we tried titrating down
3 | the Robinul. It didn't work. Then we went to scopolamine,
4 | and she seems to be doing well with that. She's the only
5 | patient where we've switched the drugs. We're due to see
6 | her in six months. We haven't had a phone call and the
7 | mother is reliable. So, that seems to be working for her.

8 | Just to underscore the point that thickened
9 | secretions are especially important in the tracheotomy
10 | patients.

11 | I put this slide up. This is the particular
12 | young lady. She had a sublingual mass. We did four duct
13 | ligations, tried to take out her submandibular glands.
14 | She's very retrognathic, so we couldn't do that. We tied
15 | off Wharton's duct. She still had some drooling, enough
16 | that it was causing a problem in terms of the secretions
17 | coming through the trach in particular and drooling over
18 | the lip and macerating the skin.

19 | So, I thought it would be reasonable to go
20 | ahead and start her on the Robinul because it was a
21 | suboptimal surgical outcome. We kept titrating it up to
22 | the point where then we started having significant problems
23 | with mucus plugging. We, of course, routinely take care of
24 | the humidifier and whatnot, but dialing down the Robinul
25 | has worked.

1 Two of our patients failed initial
2 glycopyrrolate therapy. The way that's determined is
3 minimum 3 to 6 months of glycopyrrolate therapy with
4 oromotor exercises. They have to be seen by the team, and
5 everyone on the team has to agree that surgery is an
6 option. Even so, I start with offering the surgical
7 procedure where there's the least invasion, which would be
8 the four duct ligation.

9 To review, surgical management, four duct
10 ligation involves tying off Stensen's ducts and Wharton's
11 ducts.

12 The next step would go on to take out the
13 submandibular glands, along with ligation of the parotid
14 ducts.

15 The third procedure is Wharton's duct
16 relocation. Basically what you do is dissect the
17 submandibular ducts off the floor of the mouth and insert
18 them into the tonsillar pillars. Later on you should take
19 out the sublingual glands. It becomes an extensive
20 resection because these kids are predisposed to getting
21 salivary gland cysts, ranulas, because you disturb the
22 interruptions between the sublinguals and the submandibular
23 glands.

24 Tympanic neurectomy should be up there. That
25 entails basically lifting up the eardrum and cauterizing,

1 cutting the Jacobson's nerve in the middle ear.

2 I also make a distinction between drooling and
3 aspiration. Of those procedures, really bilateral
4 submandibular gland excision with bilateral ligation of the
5 parotid ducts is the only procedure you could offer to
6 someone that's aspirating.

7 The last procedure I include is laryngeal
8 diversion. I do have several patients that have ended up
9 in the ICU in septic shock because of the aspiration
10 pneumonias. I don't think that we'd reduced the amount of
11 saliva produced significantly to prevent that if we just
12 took out the submandibular glands.

13 So, having said that, we've had three patients
14 go on to surgery. One patient had four duct ligation and
15 did not improve at all. One patient had four duct ligation
16 and improved.

17 Both of these patients are currently on
18 glycopyrrolate and improved, which is an important caveat.
19 A lot of the times, this is going to end up being combined
20 therapy. Surgery is not going to be a "fix it" as well.

21 I've had to do a laryngeal diversion on one
22 patient, and that was basically someone that ended up in
23 septic shock multiple times, basically had consolidation of
24 their lung from the multiple recurrent pneumonias. This
25 child did not speak, and basically what I did was separate

1 | the airway from the esophagus. The quality of life of the
2 | child is significantly improved, no more hospitalization
3 | for pneumonias.

4 | He's still having difficulty getting rashes.
5 | We're going to address the issue of drooling by taking out
6 | his submandibular glands and tying off his parotid ducts.
7 | Robinul has failed completely on him, and he is receiving
8 | maximal therapy at this point. Obviously, we would have
9 | done that. He really is not a candidate for oromotor
10 | exercises because of his mental status.

11 | Like I told you, that gentleman is now
12 | scheduled for bilateral submandibular gland resection with
13 | parotid duct ligation.

14 | DR. CHESNEY: Thank you very much.

15 | I think we'll hear from Dr. Hays, and then
16 | we'll have questions for the last three speakers. Dr. Hays
17 | is going to discuss assessment and methods for capturing
18 | information from the patient.

19 | DR. HAYS: Thank you. It's very nice of you to
20 | invite me to come here from Seattle. I must say when Dr.
21 | Mathis invited me to come, I mentioned to her I'm not a
22 | drooling expert. And I suppose you could take that several
23 | different ways.

24 | (Laughter.)

25 | DR. HAYS: But I am interested in disability

1 related research and spend a fair amount of time with
2 cerebral palsy patients. I thought it would be useful to
3 talk a little bit about assessment methods. I think of it
4 in two ways: capturing information that will be useful as
5 outcome measure for clinical research and also gathering
6 information for clinical care.

7 Let me start just briefly by talking about some
8 of the minimum information that's probably useful in
9 developing clinical trials for this type of an intervention
10 for children with cerebral palsy. I think that there's a
11 minimum database that could be useful and then a number of
12 other outcome measures that are more or less precise in
13 terms of their ability to capture this information.

14 The first is a demographic database. There's a
15 very nice example of that was promoted by Peter Blasco. It
16 gives some background information about every child who is
17 likely to encounter this problem and require intervention.

18 Then sort of historically there are a number of
19 different outcome measures that have been described that
20 will help to understand the quantification of drooling and
21 its impact of the child. I thought it would be useful to
22 go through each one of those very briefly.

23 Let me go to the next one and just show you
24 Peter Blasco's minimum database. It talks about the
25 information that would be necessary to provide the

1 appropriate background in entering a patient into a study
2 to look at the control of drooling. It has to do with the
3 basic demographic information and then a number of other
4 issues that are related to their method of eating, their
5 positioning, their nutritional status, dental status,
6 medications, et cetera. This is kind of the minimum
7 background database that would be useful in obtaining
8 information from the patient.

9 The next is going back historically a little
10 bit to talk about the quantification of drooling. Before
11 Dr. Mathis asked me to come, I didn't know as much about
12 drooling. I know a little bit more now. Looking back 25
13 years, I've learned it is possible to measure the flow of
14 saliva and also to measure the amount of drooling by using
15 a radioisotope. This is a study that was done more than 25
16 years ago in Sweden using a radioisotope assay. It
17 involved the intravenous injection of isotope, then the
18 extraction of saliva from the mouth, and the weighing of
19 bibs and running them through a scintillation counter.
20 It's a very accurate, precise way of measuring saliva flow.
21 But as Janet Camp-Bruno has suggested, the actual
22 measurement of saliva flow is quite possible but, in fact,
23 probably irrelevant in these types of studies.

24 The next is a Canadian study that looked at the
25 actual quantification of drooling, not so much saliva flow,

1 but actual drooling. This was done by two bioengineers who
2 I think liked making little devices. So, they devised a
3 cup/bonnet collection method with a vacuum extraction pump
4 and a collection chamber. They devised a way to collect
5 data every 15 minutes at least 10 times a day and were very
6 accurate at quantitating drooling. Again, very accurate,
7 very useful for the quantification of drooling, but it has
8 very little relevance to the patient.

9 The Teacher Drooling Scale you've read about in
10 the information that's been provided for you. I think this
11 is again probably one of the most useful tools, and it is
12 less precise but I think more patient friendly and probably
13 is a little bit better at describing the actual impact of
14 the problem for the individual patient. It's a five-point
15 scale and information can be collected by a parent, a
16 caregiver, a teacher, and it is most useful if it's done in
17 a standardized fashion.

18 A much more precise way, but again much more
19 labor intensive, is the next which is time sampling. If
20 you're familiar with this type of research, time sampling
21 usually requires an enthusiastic graduate student who is
22 willing to have a metronome in his or her ear and then will
23 actually measure behavior on 20- or 30-second intervals and
24 do it over 40 data points per session. Also, this is a
25 time sampling technique that was again used by Janet Camp-

1 Bruno and is very useful, but again extremely labor
2 intensive and expensive.

3 Behavioral and Medical Rating Scale. This is
4 kind of an adjunctive measurement tool that can be used to
5 add in the additional information that you get after you
6 quantitate drooling or have some idea about the actual
7 amount of the problem. It is not a substitute for a
8 careful investigation or access of adverse events, but it
9 can provide sort of day-to-day, hour-to-hour information
10 about what's happening in conjunction with the intervention
11 and the use of the medication.

12 A parent report questionnaire has been used by
13 Peter Blasco and his group very effectively I think.
14 Again, it requires some thought in the development of the
15 questions that are provided, but it's a good example of the
16 fact I think that parents are probably the most likely to
17 be able to accurately identify the effects of the treatment
18 and are going to be most probably relevantly committed to
19 the outcome of the patient.

20 So, the four important domains that should be
21 present in a parent questionnaire are, of course, the use
22 of the medication because it can be quite variable.
23 Parents need to be given very specific guidelines about
24 understanding and reporting side effects. The Teacher's
25 Drooling Scale can be used in a parent questionnaire just

1 as well as it can be in a more institutional setting. And
2 there has to be information about the discontinuation of
3 medications, the reasons for that, and the possible adverse
4 events that are associated with those.

5 Let me talk a little bit about a tool that has
6 not been used to this date in the evaluation of drooling
7 and it may be useful. This is goal attainment scaling.
8 Goal attainment scaling is becoming I think more and more
9 popular in disability and related research because it not
10 only talks about the effect of the intervention, but also
11 the value of that intervention on the individual patient.
12 As we become more aware of the effect versus benefit aspect
13 of doing disability research, I think we're interested in
14 not only documenting that your intervention has an effect,
15 but also that it has some relevance to the individual
16 patient. I think ethically, as I'm sure our ethics
17 consultants can tell us, that relevance is best described
18 by the patient or the person who is best able to describe
19 the best interests of that patient.

20 Goal attainment scaling allows a patient or a
21 parent to identify at the outset what they would prefer to
22 have happen as a result of the intervention. It gives them
23 an opportunity to identify their own goals. Then through a
24 series of questionnaires over the course of the
25 intervention, they're allowed to explore whether or not the

1 treatment has actually helped them to accomplish these
2 goals. It also has a part built into it so that you can
3 attach value to the goals so that there's a minus 2 to plus
4 2 rating scale that helps you to understand whether or not,
5 if there are a number of different competing and compelling
6 issues, those that are most important to the patients were
7 the ones that were actually the outcome of the
8 intervention. So, goal attainment scaling is an attempt to
9 increase the understanding of the benefit to the patient,
10 as well as the effect on the patient.

11 Then this is the last thing I want to share
12 with you. I think what you're hoping for me to say is that
13 this is the way that we can communicate with a nonverbal
14 patient and get an idea about what adverse events are. I
15 don't really have an easy answer to that question. Very
16 briefly, I think especially in the pain literature, if you
17 look at the work of Donna Wong and Mo Pomietto and people
18 like that, there are a number of relatively crude analog
19 based scales that will help you to assess pain in a
20 nonverbal patient. But I think that getting this
21 information is not necessarily easy and doesn't lend itself
22 very well to quantitative analysis.

23 However, I think that it's probably safe to say
24 that the person who is best able to represent the best
25 interests of the child, the person who is probably best and

1 most invested in the intervention and in having accurate
2 information about the child is the parent, is the family
3 member.

4 Let me just briefly take you through this
5 communication tool that we've begun to use with I think
6 some intriguing results in some of our studies.

7 We call it the decision-making and
8 communication tool. It's based on the Johnson, Siegler,
9 Winslade method of ethics case analysis. Some of you who
10 are familiar with that little primer about clinical ethics
11 are familiar with this idea.

12 But the purpose of this tool is to take history
13 taking and information gathering and break it down into its
14 parts. We talk about a four-box method here.

15 The sort of northwest corner, called medical
16 indications, is where we capture information about the
17 actual physiologic effect of an intervention. We also use
18 that box in the communication to give the family
19 information about what to expect from this drug, what to
20 expect from this treatment, what are the risks, what are
21 the benefits, that sort of thing.

22 The sort of northeast corner there is called
23 patient preference. This is where it's pretty much a
24 reminder for the clinician to find out what the patient
25 really wants, which sometimes can get lost. It helps us to

1 understand whether or not this intervention is really going
2 to be relevant to this individual patient. So, it forces
3 you to take some time to find out whether or not the
4 patient really wants this intervention, what their
5 expectations really are.

6 The sort of southeast corner is called
7 contextual issues. Contextual issues is something that
8 also needs to be included in any kind of clinical research
9 and is often not paid enough attention. What is the
10 context in which this intervention is going to be played
11 out? Is this a child who is in school, who is not in
12 school? Is this an adult? Does drooling affect his
13 interactions in a social realm? Does he have a social
14 life? Does he have a vocation? So, the context helps to
15 fill out some of the background of where this treatment is
16 going to affect this person's life.

17 Quality of life is where we allow the patient
18 or the person who can speak in the best interests of that
19 patient to determine whether or not this treatment has
20 really affected this patient's quality of life. This is
21 not an easily quantitative tool, but it's very, very
22 useful, we find, in improving both patient and provider
23 satisfaction. I think it helps us to be able to capture
24 again, as I said before, the effect and the benefit of the
25 intervention. We'd like to be able to use this to a

1 greater extent in clinical research around disabilities.

2 Thanks.

3 DR. CHESNEY: Thank you very much.

4 Questions for Dr. Wilfond, Dr. Pena, and Dr.
5 Hays. Dr. Danford.

6 DR. DANFORD: It seems to me we could make our
7 investigation a great deal easier if we could select only
8 those patients who have sufficient cognitive and
9 communicative skills to let us know about the response to
10 the medicine and the side effects reliably. But I have
11 some worries about that.

12 The first is availability of such patients.
13 Does drooling occur sufficiently frequently in patients who
14 have communicative skills to allow a sufficient population
15 to be available for study?

16 Secondly, are communicative patients with
17 drooling representative of the population as a whole?

18 And third, is it ethically sound to selectively
19 subject these patients to the risks and benefits of the
20 research?

21 DR. WILFOND: In your last question, you were
22 referring to selecting which patients?

23 DR. DANFORD: The ones with the highest
24 communicative skills.

25 DR. WILFOND: I think my short response to all

1 three questions is that a majority of the patients who have
2 swallowing dysfunction who have significant problems
3 drooling are able to communicate. As a way of treating
4 those patients, we also need to be able to develop the
5 skills of assessing them in a clinical setting as well.
6 So, my concern would be if research was only done in
7 patients who could communicate, we still would be lacking
8 some of the information that we would need to make those
9 clinical assessments of the children. So, for that reason,
10 I think it would make sense to do the research in that
11 broad population.

12 DR. CHESNEY: Dr. Nelson had a question.

13 DR. NELSON: I'm struck by the comment that Dr.
14 Pena made about dialing down the drugs. I have sort of two
15 questions which are related.

16 In doing that, did you feel or did the families
17 feel that they were accepting a certain level of drooling
18 that they otherwise would find unacceptable simply to avoid
19 undesirable side effects so that the real question is
20 finding that rather narrow therapeutic window between
21 effect and side effect?

22 And then the research design question comes in.
23 I'm not that concerned about limiting this to individuals
24 who can self-report since there's a lot we do in pediatrics
25 for a lot of kids that can't self-report what's going on.

1 | But then the question arises in my mind of whether there
2 | needs to be blinding as part of that assessment in a
3 | research setting, not so much between groups, but certainly
4 | given this more physiologic endpoint in a sort of
5 | randomized, crossover, blinded individual as their own
6 | control kind of study.

7 | I wonder if you could comment on both those
8 | points.

9 | DR. PENA: To the first question, when you meet
10 | the parents and the family, the child, they want no
11 | drooling. I can't tell you the number of times: Can you
12 | increase it? Can you increase it? They want no drooling.
13 | As long as they're not having any side effects, I'm willing
14 | to do it slowly and in increments.

15 | But what happens is this very situation.
16 | That's why I asked them to speak to you all. They are not
17 | going to report or won't think that the complication is
18 | secondary to the glycopyrrolate.

19 | But the children really want to stop drooling
20 | because it really makes a significant impact on their life.
21 | So, they ask me can they still stay on the glycopyrrolate.
22 | And what I've done -- and I admit it; it's two anecdotal
23 | experiences -- is go down to the dose I knew they were
24 | doing okay with and still having some drooling and
25 | basically following them out and see how they're doing.

1 With the two patients I've had that problem, we still
2 haven't had 3 to 6 months' follow-up to give you a good
3 answer.

4 But, yes, it's certainly a problem. Even
5 though I try to safeguard it by having all the
6 questionnaires and having the caregiver, as well as the
7 school, report it to make sure that the responses are as
8 consistent as they can be from as many people observing the
9 children, there are going to be problems.

10 In terms of your second question, I'm sorry.

11 DR. NELSON: It was a question about the
12 importance of blinding in making those assessments. I'm
13 also struck. What's unusual here, when we try to pick the
14 right dose, is there seems to be physiologic variability,
15 but here there will also be, relative to the last
16 presentation, variability in the judgment on the part of a
17 parent of where the drooling is acceptably controlled and
18 the side effects are acceptable. So, we're not so much
19 picking an endpoint where there's efficacy and safety.
20 We're picking an endpoint where there's enough efficacy and
21 not that much side effects. So, it's almost a different
22 endpoint than our normal clinical trials. But the point is
23 blinding in that assessment to know that we're getting data
24 that's not influenced by the bias about the medication.

25 DR. PENA: Well, I agree but I don't know how

1 we go about doing it.

2 DR. NELSON: Well, you could simply spend 2
3 weeks on a blinded medication, 2 weeks on the other part,
4 so just do a sort of dummy back and forth so that with
5 blinded assessments, you begin to find is where is that
6 child's balance and do it over enough kids that you can
7 begin to draw some conclusions, rather than just using the
8 medication and then randomize between groups because I
9 think it would be hard to justify leaving a kid on a
10 placebo to get that.

11 But I don't think it's so much from the
12 standpoint of efficacy as it is from knowing that you have
13 a fair evaluation of the endpoints, particularly if you're
14 using, which I agree would be more useful, the drooling
15 scales, the BMRS, the parent report questionnaire, goal
16 attainment scaling, all of which I assume would be impacted
17 by the bias of the observer fairly significantly.

18 DR. PENA: I think it's a good point. I
19 suppose we could do it longer. Two weeks is really not
20 going to work on and off. I mean, there's reality.
21 They're not going to do it. It's not going to happen.
22 They'll know right away, especially if they have some
23 improvement, and they'll say, what's up? And 2 weeks later
24 they're drooling again. You can tell within 2 to 3 hours
25 for most of these patients that they're significantly

1 improved.

2 So, you're going to have two problems. One,
3 they're going to fall out of the study because they're
4 going to get discouraged and think it doesn't work. Then
5 you have the next problem. The glycopyrrolate actually did
6 help them and they don't want to participate anymore, which
7 has happened to two people that we have in the study.

8 These patients are very complicated. The care
9 of the patient, the multiple, multiple levels. I don't
10 know. I don't see in reality how it's going to work unless
11 we take 10 isolated and put it together, but can you
12 extrapolate from 10 patients and which 10 patients would
13 they be?

14 DR. CHESNEY: I think that's one of the issues
15 we probably need to address.

16 I have a question about the pharmacokinetics of
17 these drugs. Would it be more beneficial or has anybody
18 looked at the issue of giving it more frequently so that
19 one maintains continuous levels that are effective? Is
20 there a phenomenon of it takes a couple of hours to get an
21 effect and then you have a maximal effect for a couple of
22 hours and then the salivation starts again? Has
23 consideration ever been given to giving it more often and
24 maintaining maybe not such a high dose?

25 Dr. Fink.

1 DR. FINK: I think obviously a continuous drug
2 would be better because with limited experience, I've used
3 scopolamine patches, and in the patients who don't get
4 neurologic side effects from the scopolamine patches, which
5 gives you 2 to 3 days at a time, it works wonderfully. But
6 unfortunately, scopolamine is the wrong drug for a lot of
7 patients. But there's no question something like a long-
8 term patch that gives you 2 to 3 days of continuous
9 efficacy probably has better biologic effectiveness.

10 DR. CHESNEY: Yes, Dr. Walters.

11 DR. WALTERS: I have a question for Dr. Wilfond
12 about selection of subjects in this research. I think you
13 made a very good point about institutionalized patients or
14 residential patients not being ideal as the first subjects
15 in such a study. I wonder if you would draw a similar
16 distinction between children who are living with their
17 long-term parents and children who are living with foster
18 parents. I don't want to stereotype foster parents. I do
19 think that there is a difference in the level of commitment
20 of parents who plan to hang with their children on a long-
21 term basis.

22 DR. FINK: Not on the ethical part of this, but
23 I think there's a real problem with that conceptually which
24 is, if you actually look at the impact of drooling,
25 drooling is one of the primary things that can lead to

1 institutionalization of many kids because it increases the
2 care needs so dramatically. So, if you rule out the
3 institutionalized patient with drooling, you're taking the
4 mildest group or the most competent parents, and that's a
5 big bias in and of itself.

6 DR. WILFOND: There are actually two issues.
7 One is the issue of the institutionalized patient and the
8 patient in foster care. Maybe I'll first respond to Bob
9 and then to Leroy.

10 I think you raise a good point, that it's
11 perhaps a different population, those children that are
12 institutionalized versus those that are not. But unlike
13 the communication issue, I guess my initial assumption,
14 which I would need to clarify, would be that the population
15 of non-institutionalized patients is probably broad enough
16 that you could still learn a lot of the information that
17 you need to learn without going to that group, whereas I
18 would be much more concerned about restricting it to
19 patients who were able to communicate and that group being
20 more skewed way to the other end.

21 With regards to the foster parents, I think it
22 also varies from state to state as far as what foster
23 parents are allowed to do legally. I really can't speak
24 directly to that. I'm not cognizant of all those issues.
25 But from an ethical point of view, I think that foster

1 | parents are as likely to be as committed to their children
2 | as other parents would be. I'm partly saying that just
3 | from my own experience of dealing with foster parents of
4 | children with disabilities. They're often in many ways
5 | more committed than the broad range of parents. So, I
6 | would actually be comfortable with the types of assessments
7 | and observations they make. Generally, when I'm thinking
8 | about clinical decisions I make with foster parents,
9 | they're usually quite capable of balancing risks and
10 | benefits.

11 | DR. CHESNEY: Ms. Woerly.

12 | MS. WOERLY: My group that I work with are
13 | medical foster, and these parents are very committed to
14 | taking care of these children. They know what they need.
15 | They know what medications they need. They can go into a
16 | clinic and tell the doctors what exactly that they're
17 | looking for. They have the kids that are drooling. They
18 | know the problems that it causes.

19 | The only problem is that the state will not
20 | allow these children to be used as research subjects.
21 | That's the biggest problem, but they would be the best
22 | ones. They are the caring people. They're really in tune
23 | and that's they're job.

24 | DR. WILFOND: They're not prohibited by the
25 | research regulations from participating. It's just that

1 | the organization in terms of foster care makes that
2 | judgment even though we could say that's perhaps a wrong
3 | judgment for them to make.

4 | MS. WOERLY: Right, exactly.

5 | DR. CHESNEY: Dr. Kodish.

6 | DR. KODISH: Ben, I thought your talk was very
7 | nice, but one area that I thought was missing that's
8 | important to talk about is assent. I think it needs to be
9 | said that purely from an ethical perspective, it would be
10 | preferable to enroll children who are capable of some
11 | degree of assent. The more, the better in the same way
12 | that traditionally we've thought it's better to experiment
13 | on adults over children.

14 | Having said that, there are times when the
15 | needs of good science and good ethics clash. While it
16 | might be ethically preferable to conduct these studies with
17 | children capable of assent, I don't think we ought to
18 | prohibit, if the needs of science are such, research on
19 | children who are completely incapable of assent given that
20 | we have caring parents who are hopefully making good best-
21 | interest decisions.

22 | DR. CHESNEY: Dr. Goldstein.

23 | DR. GOLDSTEIN: I think we've got to recognize
24 | that we're dealing with a very special subset of children.
25 | These children rarely have isolated drooling. They are at

1 | the end of the scale where they have multiple impairments
2 | and multiple disabilities, and communication is often
3 | associated with this.

4 | So, if we try to find the pure subject, given
5 | that there may be as many as 10,000 children in the nation
6 | where drooling is a meaningful problem, if we try to subset
7 | that into children who can communicate or children who are
8 | not in some kind of institutional setting because of the
9 | multiple impairments and the multiple disabilities, the
10 | scatter around the country are going to make a coherent
11 | trial extraordinarily difficult to operate in order to get
12 | reliable data with enough numbers in the numerator and
13 | denominator to give any important tests of significance.

14 | I think all the issues that have been raised
15 | are pertinent issues that need to be considered, but I
16 | would again urge the committee to consider that this is a
17 | group of children with very multiple impairments and
18 | disabilities, of relatively small numbers -- relatively --
19 | with many, many characteristics. So, if we start
20 | developing cells as to which kind of child with which kind
21 | of drooling is beneficial by any particular impact, we're
22 | going to find ourselves in a terrible numbers crunch in
23 | order to develop tests of significance.

24 | I would like to, if I may, address the issue of
25 | blinding. I'm reminded of the old biostatistical joke that

1 | if you have a supposed treatment for active rabies and you
2 | give it to one person and the person recovers, it's a
3 | miracle. If you give it to two people and they both
4 | recover, it's a trial.

5 | When the endpoint is absolute and the natural
6 | history is well known, you really don't have to blind even
7 | though blinding is a beautiful gold standard to attempt to
8 | approach, but it isn't necessarily the law of the Medes and
9 | Persians. So, one can blind observers in the sense that
10 | more than one observer makes the evaluation and tests the
11 | reliability of the observers without necessarily blinding
12 | the application of the intervention.

13 | The only reason I bring this up is again to my
14 | original point. We're dealing with a relatively small
15 | cohort of children with multiple, multiple problems. These
16 | problems are going to affect the impact of the medication
17 | because they do have upper motor neuron lesions primarily.
18 | They have all of the characteristics of upper motor neuron
19 | lesions, and they're a very tough group of kids with many,
20 | many problems.

21 | DR. CHESNEY: Thank you.

22 | Any other questions for our speakers? Dr.
23 | Fink.

24 | DR. FINK: More a question I guess maybe going
25 | back to Dr. Kelsey. It would seem to me that this

1 | discussion, since we're talking about drugs that are
2 | already licensed for this indication in adults, that we
3 | really do not need to talk about an efficacy trial in
4 | pediatrics, and we're really going to be talking about
5 | pharmacokinetics and dosing, safety and side effects, in
6 | which case blinding really shouldn't be much of an issue.

7 | DR. KELSEY: Yes, I would agree with that.
8 | We're looking at efficacy in the context of the adverse
9 | events, the risk-benefit ratio.

10 | One trial design that we have seen employs a
11 | placebo control. What was done in this proposal is that
12 | the patients were titrated by their caregivers over a
13 | period of weeks to what they considered to be an optimal
14 | level based on the side effects. They would basically
15 | increase the dose until the side effects became intolerable
16 | and then dropped down. Then once a dose had been
17 | established for that patient, then they were randomized to
18 | either placebo or drug. We're not particularly wild about
19 | that design, but that's one that we've seen where you could
20 | use a blinded design. It would be different than the
21 | crossover that was proposed earlier.

22 | But to answer your question, we're really
23 | interested in efficacy only in terms of the risk-benefit
24 | ratio.

25 | DR. FINK: This is a drug or a class of

1 | compounds where we're willing to extrapolate the adult
2 | effect to pediatrics, and there's really no reason, unlike
3 | yesterday, to question whether the pediatric effects would
4 | be markedly different in terms of efficacy.

5 | DR. KELSEY: We believe that these
6 | antimuscarinics work in kids. The doses may be different,
7 | but the effect is the same.

8 | DR. CHESNEY: I'd like to go ahead. Could we
9 | save that for our discussion later?

10 | DR. NELSON: Yes.

11 | DR. CHESNEY: Thank you.

12 | Our next speaker is Dr. Scott Stiefel to give
13 | us the perspective of the American Academy of Pediatrics.

14 | DR. STIEFEL: Greetings from Utah. I both
15 | recognize and appreciate the privilege to address this
16 | committee today.

17 | I probably need to talk about my biases. Being
18 | a pediatrician and adult psychiatrist and been involved in
19 | the care for the last 10 years of only kids with
20 | developmental disabilities and also being probably about
21 | the only person in the country who is both on the clinical
22 | research side of the university but also the medical
23 | director for a state human services agency, what you're
24 | going to hear today is a reflection of that broad range of
25 | biases.

1 I've also been given a dual charge: one, to
2 talk about what the American Academy of Pediatrics'
3 Committee on Children with Disabilities thinks in regards
4 to drug studies in general and particularly in regards to
5 these issues, and also to share some clinical experience in
6 regards to what is really going on with this population,
7 which I think continues to come up as one of the major
8 issues.

9 The big picture is that we strongly support
10 meaningful studies of all medications used in children,
11 particularly those vulnerable children with special needs.
12 I think it's absolutely critical to realize that
13 indications in kids without special needs are not always
14 applicable to children with disabilities. So, to add
15 another layer, we have to look at not only just indications
16 in children, but indications in the appropriate groups.

17 In general, the studies must address all the
18 things that we've talked about. But I want to add one new
19 concept, that adverse effects must be presented in children
20 in a developmental context, and I'll talk more about that
21 in the future.

22 Again, I think what we're talking about is not
23 efficacy studies, but we're talking about a paradigm shift
24 that must be made in terms of how we look at the study of
25 these medications. That's partly why I came here today

1 | because this is a great microcosm to be able to extend to
2 | not only this issue, but all medication studies in children
3 | with special needs.

4 | What is critical is to look at some subgroup
5 | differential response. In this population, look at issues
6 | of polypharmacy.

7 | Also to make choices between medications in the
8 | same class. We don't study that and we have to start
9 | studying those things.

10 | Then again, how do we make choices between
11 | different therapies? The literature does not help us with
12 | this to a very great extent.

13 | The multiple ethical issues have already been
14 | explained and I'm not going to go into those.

15 | This topic also presents an unusual and complex
16 | set of issues. Again, what we're talking about is a Zen-
17 | like balance that must exist between inhibition of saliva
18 | production and adverse effects, again realizing that saliva
19 | production is not the major issue in terms of rate. Our
20 | literature clearly, in terms of critical review, lacks
21 | scientific rigor and provides little comparison between
22 | these different interventions. These children have complex
23 | pathological and adaptive functional assessment, and their
24 | needs are very complex. There are many etiologies and
25 | mechanisms which create the subgroups.

1 Even though some have been presented, we have
2 no truly quantifiable measurement techniques. That has
3 been pretty well talked about, so I'll move on. But there
4 also exists I think in the literature regarding this a
5 general pessimism about pharmacological management. In
6 your references, I've also put articles in that are more
7 optimistic towards pharmacological management.

8 Again, all the things that people have said
9 before, but what is clearly important is polypharmacy in
10 this population. We're going to talk a lot about it.

11 Now, you open any pharm textbook, anything
12 else, this is the anecdotal information that exists.
13 Infants and young children are especially susceptible to
14 toxic effects of these medications. There's a need for
15 close supervision of infants and children with CP and other
16 forms of brain damage when giving these medications. And
17 increased response to anticholinergics has consistently
18 been reported in children with disabilities, again with the
19 dosage adjustments that we've been talking about. This is
20 anecdotal, folks, though, and we have to look at where this
21 came from.

22 Again, I think we have to also not just study
23 these medications, but understand the whole spectrum of
24 things that lead to this, which include speech problems,
25 feeding and swallowing difficulties, structural and motor

1 | problems, upper respiratory congestion, and of course
2 | aspiration at one end of the extreme.

3 | What we have to do, when we're assessing
4 | etiology, is we really have to look at all these different
5 | things. Again, this drug has action only on rate of saliva
6 | secretion. So, again, there are a lot of things that go
7 | into it, the cognitive appreciation of the salivary spill
8 | and all the other things that folks have talked about.

9 | Therapies also have to be hierarchical in
10 | nature, in other words, with the least invasive first,
11 | everything from behavior modification to surgery. I think
12 | you brought up a critical point that's not established in
13 | the literature, which is that many times multiple things
14 | have to be used at the same time.

15 | The epidemiology we know. As you can see, 10
16 | to 30 percent is a broad range in regards to drooling
17 | problems in cerebral palsy, but I also appreciate the fact
18 | that other people have talked about that we're not just
19 | talking about cerebral palsy. In fact, we're talking about
20 | a broad range of kids. We see a mixed population which is
21 | very unusual to see everything from birth to death. We've
22 | been doing the medical home model for over 10 years in
23 | terms of coordinating mental health and pediatric care and
24 | habilitative services for these folks. Again, we don't
25 | have a clue what the percentage of drooling is in severe,

1 | profound, and moderate mental retardation. We just don't
2 | have any help in the literature.

3 | This might not be popular, but the reality is
4 | that the gap between incidence and prevalence in
5 | developmental disabilities is closing. What this means is
6 | that we're saving more of these kids and the numbers are
7 | actually increasing. The complexity of these children is
8 | also increasing dramatically as is the life span, which
9 | brings other issues into this. Again, the expectations of
10 | children that are now living and being integrated into our
11 | communities and schools are also increasing.

12 | These are the kids we actually are talking
13 | about. I really want to talk about that. These kids have
14 | central nervous system developmental problems or damage
15 | that translates into a developmental disability or mental
16 | retardation. In addition, almost all the kids we see have
17 | other chronic central nervous system illness such as
18 | cerebral palsy, epilepsy, movement disorders. All these
19 | kids pretty much have multiple chronic general medical
20 | illnesses. Most of these kids have sensory and
21 | communication challenges. There's a new field of comorbid
22 | mental illness in this population which also needs to be
23 | looked at. It has significant impact. And many of these
24 | kids also have severe behavior problems. This is actually
25 | the population we're going to be studying, folks, and I

1 think the comments about trying to just choose folks who
2 have no communication problems and no cognitive disability
3 are very appropriate. Obviously, our recommendations are
4 that you can't do that.

5 These kids have fragile brains.

6 The average kid in our clinic, unfortunately,
7 comes to us -- we're the bottom of the drain -- on six to
8 eight medications which have central nervous system
9 activity. Polypharmacy is horrendous. Two to four of
10 these medications, depending on which subgroup we're
11 looking at, have additive anticholinergic activity, and
12 we're talking about adding a third or fourth medication to
13 that. 70 percent of the kids have behavior problems that
14 are the mode of presentation, and they have two or more
15 medical problems that have not been recognized or
16 appropriately treated that add to their behavioral
17 presentation. In our population, which is about 2,500 kids
18 and adults, about 1.5 to about 5 percent, depending upon
19 the subgroup, are on drooling medications.

20 I don't want to go over this, but I want to
21 point out a couple of things that we're beginning to see
22 emerge.

23 First of all, the gastrointestinal comments I
24 think are clear. The only meaningful thing I do in my life
25 is treat constipation. It's the one thing that makes more

1 | difference than just about anything else I do.

2 | (Laughter.)

3 | DR. STIEFEL: The other thing we're beginning
4 | to see is a tremendous worsening of gastroesophageal
5 | reflux, which is a problem in this population. We know
6 | that these medications have effect on the sphincter and
7 | other sorts of things, so the physiology also is correct.

8 | The other thing is that most of these kids --
9 | and a lot of them have severe pulmonary problems. Again,
10 | it's a very complex sort of chain of events and vicious
11 | cycle that you get into with these kids.

12 | The other problems that we're beginning to see,
13 | as we're starting to study sleep disorders in kids with
14 | disabilities, are that none of these kids have normal
15 | regulation and architecture, and these medications can
16 | further affect sleep regulation. It's a major, major
17 | issue.

18 | Then the last thing is my bias is you can't
19 | separate the brain out into central nervous system and
20 | psychiatric problems, general medical problems, but there
21 | are tremendous psychiatric implications of these
22 | medications.

23 | How can we look at adverse effects? Well,
24 | again, what you have to remember is that adverse effects in
25 | this population are going to mostly manifest as behavior

1 | changes, particularly in a limited verbal status.

2 | Assessment must first provide an understanding
3 | of the child's learning strategies and degree of cognitive
4 | disability. If we don't understand how the kid experiences
5 | the world, we can't study him.

6 | We then have to establish a relationship with
7 | that child and the family and a shared communication
8 | strategy with that child. That doesn't have to be verbal.
9 | There are many ways to communicate with kids.

10 | We also have to objectively be able to assess
11 | pain and discomfort, and that's been well presented.

12 | This is the other kicker. All the diseases
13 | that were on that last slide don't show up in 2 weeks.
14 | These are things that take sometimes months and years to
15 | ramp up, and then after they've ramped up, they take
16 | sometimes months and years for the parents or caregivers to
17 | recognize that it's a problem. So, it's a real challenge
18 | in regards to seeing these folks. I introduce the concept
19 | of these disease cycles that we get into. These studies
20 | are going to have to be of significant length using
21 | outcomes tools to be able to look at these issues, if
22 | that's really what our charge is.

23 | Behavior. How do we quantitatively assess it?
24 | Well, you've had some tools, and I'll give you some more.
25 | But remember all symptoms usually are behavior changes.

1 Behavior is usually the symptom when the child is having
2 pain or discomfort, having many times symptoms of general
3 medical conditions, many times symptoms of mental illness,
4 and again many times symptoms of iatrogenic side effects.

5 In these kids, you have to have a multi-
6 disciplinary or interdisciplinary, whatever word we're
7 using this month, assessment --

8 (Laughter.)

9 DR. STIEFEL: -- that includes medical
10 evaluation, developmental analysis, a functional analysis
11 of behavior which is a scientific tool that we use, and
12 then a use of many of the rating scales that we use to
13 provide both data for assessment and evidence of change and
14 tracking.

15 I've already made this point. It should be
16 obvious at this point in the history.

17 Safe and ethical conduct. Well, this is a
18 vulnerable population. It is our responsibility to
19 protect. The point I want to make is part of that
20 responsibility is demanding meaningful studies, which is
21 what we're doing.

22 The need for multidisciplinary team assessment.
23 I keep saying that. That means it must be important. I'm
24 a little bit perseverative to those who know and love me,
25 but it is an important thing. You can't do this without

1 the expertise and without understanding this population.

2 We also need agreement in terms of forming the
3 database for description of etiology, pathology, and
4 subgroups. Not that we're going to necessarily separate
5 the subgroups in terms of studying them, but we have to
6 actually know what the other issues are and what the other
7 interventions are. We have to look at, somewhere down the
8 road, subgroup response patterns so that we can get into
9 making more meaningful recommendations as to when these
10 drugs can be used. And then we must study, again, the
11 etiologies.

12 I already talked about the increase in length
13 of time. I'm saying it again. You can't do this over the
14 short term.

15 The other thing is that in the literature there
16 is some talk that some of these medications can also form
17 tolerance issues, and we're going to have to look at
18 significant length of time. You know, the brain and the
19 body up and down-regulate things in response to what's
20 done. So, we have to look at that in terms of
21 discontinuation, whether that's tolerance or whether there
22 are other things that go into that.

23 We have to establish and support and promote
24 research in the consortiums that look at these issues, and
25 then again all the other ethical issues that go with this.

1 I agree with comments that were made earlier
2 about IRBs, but we must also include state and local
3 disability human services rights oversight. We cannot look
4 at those boundaries that many times are imposed and not
5 address that. We have to look at that and we have to start
6 to involve those folks. In all of our studies, we actually
7 involve those. That's partly why I'm the medical director
8 for the human services agency, so we can get away with it.

9 (Laughter.)

10 DR. STIEFEL: It's critical I think that we use
11 independent assessors. That doesn't mean not use the
12 caregivers, but we clearly have to use independent
13 assessors also, to come back to some of your questions.
14 And we can address that later.

15 The other part that's always missed in kids
16 with disabilities is that you have to always include the
17 child, adolescent, or young adult regardless of their
18 cognitive disability, regardless of their cognitive
19 strategy. There hasn't been one kid I've ever taken care
20 of that I can't develop a relationship with and get
21 information from. You have to include the kids in this.

22 We need consensus definition and assessment in
23 regards to the significance of the impairment -- and that's
24 been talked about -- and the etiology.

25 Quantification of volumes. There are a lot of

1 | systems out there." The newest is Chin Dry System which is
2 | going to come out of the Texas folks. But again, that's
3 | only one small part of the problem, and again, this is a
4 | very complex issue.

5 | We also need consensus as to the degree of
6 | impairment caused by drooling. That's one thing about
7 | which we still have huge issues getting consensus as to
8 | what is the degree of drooling. The reality is it's a
9 | different thing for each kid and a different thing for each
10 | family, and that's really where the challenge is.

11 | I also believe that we must identify
12 | medications with good efficacy and good side effect/benefit
13 | ratios. That's, of course, a summary statement.

14 | Again, more support for studies that are
15 | broader range, more meaningful in terms of the drug choices
16 | and polypharmacy.

17 | My recommendations and our recommendations for
18 | formulations. Many of these kids have swallowing
19 | difficulties, of course. Oral forms are an issue there.
20 | Whether or not you realize it, giving a medication five
21 | times a day is extraordinarily disruptive to a child's life
22 | and a family's life. So, we have to think about those kind
23 | of things.

24 | Transdermal. I hospitalized three kids last
25 | year after taking Catapres patches. These kids put things

1 | in their mouths and they chew them. So, we have to look at
2 | transdermal applications and the safety issues.

3 | Pharmacokinetics. Of course, we have to do
4 | pharmacokinetics. We know kids are not little adults. We
5 | have to do it.

6 | Things like quaternary amines, glycopyrrolate,
7 | that we look at, only have absorption of 25 percent. So,
8 | huge issues in regards to these issues.

9 | The blood-brain barrier. There's a very
10 | interesting part of research right now. What you will
11 | recognize is that a lot of these kids with the severe CNS
12 | problems they have, though, have ongoing insults and
13 | variable intactness of their blood-brain barriers. That's
14 | true in hydrocephalus, kids with chronic epilepsy, immune
15 | disorders, self-injurious behavior, and other sorts of
16 | traumatic brain injuries. We're talking about using drugs
17 | like glycopyrrolate that don't cross a blood-brain barrier.
18 | I'm making the point that these kids' blood-brain barriers
19 | are variable.

20 | We also -- again, just to punctuate -- need
21 | broad titration and dosage latitude. Again, I really
22 | applaud this committee. We're not going to address this
23 | retrospectively. We're going to do it on the front end.

24 | Medications should not be extemporaneously
25 | formulated.

1 Again, polypharmacy sort of raises its head in
2 this group.

3 Again, guidance in dosing, other issues. I
4 believe that we have to have discussion of adverse events,
5 the additive polypharmacy, the general medical and
6 psychiatric problems that can lead to recognition of
7 adverse events, and again the titration schedule.

8 Other therapies must probably be looked at
9 because it's not all commonly known in the people who will
10 use these medications. Not that we will make
11 recommendations, but that discussion needs to occur in the
12 literature that we provide with these medications.

13 I am going to make a strong statement, though,
14 that dental recommendations actually need to be made for
15 these kids. When we cut down saliva production, we have to
16 not only do prevention, but we also have to do
17 recommendations for surveillance and intervention. The
18 caries in these kids and the dental care just become quite
19 profound sometimes. Again, that's a longer term cycle that
20 we have to look at.

21 Then I'm also going to challenge you that all
22 of us physician types are now using electronic management
23 software for medication interactions and other sorts of
24 things. I would encourage interface between FDA and some
25 of the people who are putting these kinds of things out as

1 a way to actually look at the polypharmacy.

2 Other issues? Thank you.

3 DR. CHESNEY: Thank you very much.

4 Our next speaker is Dr. Murray Goldstein who is
5 going to give us an overview of the scope of the problem.

6 DR. GOLDSTEIN: I've been asked to address the
7 problem from the perspective of a family based
8 organization, United Cerebral Palsy. Within the
9 organization, there is a second organization known as the
10 Research Foundation in which we attempt to address the
11 biomedical issues relevant to developmental brain injury,
12 specifically cerebral palsy.

13 To repeat some of the numbers that you've
14 already heard, the best estimates at the moment are that
15 there are about 500,000 persons in the United States with
16 the syndrome referred to as cerebral palsy. These are
17 fairly loose and thin data because cerebral palsy is not a
18 reportable disorder. We don't have Framinghams and
19 Tecumsehs to help us. However, when we do extrapolate from
20 the Scandinavian data, they are so remarkably similar to
21 our own experience that, extrapolating from that, we still
22 come up with about 500,000 persons in the United States.

23 We also are reasonably comfortable that of the
24 500,000, about 200,000 are under the age of 20. So, we're
25 dealing with a population which is characteristic both at

1 the children side and at the adult side. Of these 200,000,
2 it is estimated that there are about 20,000 with
3 significant problems of drooling that does interfere with
4 quality of life.

5 Will this population grow? Well, it is
6 growing. Within a decade, we have gone from an incidence
7 rate of 2 per 1,000 live births to 2.8 per 1,000 live
8 births, and it looks as if those numbers are steadily
9 increasing.

10 Why are they increasing? The wonders of
11 neonatology. The low birth weight infant now of 1,000
12 grams has a reasonable probability of surviving. The
13 infant of 1,500 grams will certainly survive, and about 30
14 percent of these infants do have developmental brain damage
15 right in the neonatal nursery. So, we're facing into an
16 ever-growing problem that will affect us both not only
17 medically but as these children enter the school system and
18 in later years into the work place. So, we can look
19 forward to that.

20 Secondly, the wonders of the ability now to
21 have infertile relationships become fertile, and we do know
22 that this usually results in multiple births, again a major
23 risk factor for developmental brain damage.

24 So, on each end of the spectrum -- the very
25 small infant, the mother with more than one fetus -- we can

1 | predict that this problem is going to get worse. So, we
2 | have to look forward to the issue of how do we intervene as
3 | a society to address these problems and particularly in
4 | that cohort of multiple disabilities.

5 | As physicians we too often look at the issue of
6 | impairments. We like physiologic measurements. It's easy
7 | to tangle with and we grow up in the world of impairments.
8 | But parents don't think of impairments. They are not
9 | really, really concerned with spasticity; they're concerned
10 | immobility. They're concerned with drooling; they're not
11 | concerned primarily with whether the ducts are working
12 | properly. So, disability becomes a major, major factor
13 | when you look at it from the parental or caregiver's
14 | viewpoint, and certainly as these children develop their
15 | own personalities, they are also concerned with their
16 | disabilities and not their impairments, which is why the
17 | World Health Organization, the National Center for Medical
18 | Rehabilitation Research have come up with these patterns of
19 | being able to describe this complexity of interactions.

20 | A point that I did try to make in response to
21 | one question is we are dealing with a population of
22 | multiple disabilities. It is relatively rare that we're
23 | looking at a child whose only major problem is salivation.
24 | Well, salivation is not the problem; it's drooling. Thank
25 | God they're salivating, given the problems that would be

1 associated with the lack of salivation. So, we're dealing
2 with a small cohort of children with multiple disabilities,
3 and it becomes a technological tour de force to put this
4 population together and come up with meaningful numbers so
5 that we can get some sense of statistical significance
6 about the importance of any intervention.

7 Thirdly, whether we like it or not, these
8 studies are going on all over the country. They're going
9 on in physicians' offices, in clinics all the time with
10 very biased populations and with very biased observers.
11 They're trying to do their clinical job, and doing it well,
12 but they recognize full well the population they're seeing
13 does not represent the population of droolers, and their
14 approaches don't necessarily represent the population of
15 different approaches.

16 So, for the benefit of these children and of
17 their parents, the caregivers, we must approach it from a
18 national viewpoint with a trial because in addition to the
19 trial and the specific data we will get addressing the
20 question, we're going to be able to begin to address this
21 population and its characteristics if the population is
22 broad enough and big enough. And only through a national
23 effort can we do this.

24 Finally, my plea to the FDA is I recognize your
25 responsibilities as a regulatory agency. On the other

1 | hand, close collaboration and cooperation with other
2 | government and nongovernment agencies is imperative. As
3 | you know, a new national center for birth defects and
4 | developmental disabilities has just been put into place by
5 | law, and now with an acting director, in the Centers for
6 | Disease Control. It has a \$60 million budget. Those of us
7 | who are working on the Hill will see that that will double
8 | in the reasonably near future. Here's an agency whose
9 | responsibilities overlap tremendously with yours because
10 | they will be the data-gathering agency. The NIH,
11 | obviously, in terms of the pharmacologic and physiologic
12 | approaches to these issues.

13 | My plea is has the time come to recognize in a
14 | positive way the overlapping responsibilities of the
15 | several agencies so that we can, in fact, work together to
16 | begin to identify some of these problems and, working
17 | together, address them rather than being forced into our
18 | own little cubbyholes?

19 | I had the privilege years ago of being an
20 | Assistant Surgeon General and working with Dr. Koop. I can
21 | tell you our conversations about this were wonderful
22 | because Dr. Koop refused to recognize that there were
23 | agencies in the Public Health Service. He felt that there
24 | were physicians and scientists who had an opportunity and
25 | that the agency role was perhaps inhibitive.

1 Finally, I urge you to incorporate the use of
2 the parents even though they are obviously biased. Thank
3 God they're biased. On the other hand, I have learned by
4 working with them that they are often the most scrupulous
5 observers of what is happening to their children, and the
6 rest of us who plug in every now and then and take a look
7 and plug out again don't really understand the natural
8 history of what's going on with that child in its day-to-
9 day involvement and interaction. So, parents are superb
10 observers. Sometimes they scare the hell out of me with
11 the conclusions they come to, but they're good observers.

12 (Laughter.)

13 DR. GOLDSTEIN: So, in the observational
14 ascertainment of an intervention, parents need to be one
15 part -- not the part, but one part -- of the observational
16 data-gathering. And that's where the blinding comes in
17 rather than the children.

18 Well, on behalf of parents, on behalf of those
19 of us who are involved in the private sector looking at
20 exactly the same problems, welcome aboard.

21 DR. CHESNEY: Thank you very much, Dr.
22 Goldstein. Having attended a conference by default
23 recently on family centered care, I've become much more --
24 not the pediatricians, in general, are very focused on
25 parents, but it's a paradigm shift to think about family-

1 centered care as opposed to care that we give for families.

2 Well, we're very fortunate and grateful this
3 morning to have Ms. Hurlburt here to speak to us, and we
4 look forward to hearing your comments.

5 MS. HURLBURT: Thank you. Be patient with me.
6 I've never spoke in front of a large medical group, and I
7 can't believe I haven't asked questions already.

8 I'm here to represent my daughter, Ronny-Kay,
9 who by choice came with me today to be my support because I
10 always support her.

11 RONNY-KAY: Hi.

12 MS. HURLBURT: Generally speaking, she is an
13 athetoid quadriplegic with extensive drooling.

14 We are now taking Robinul. I've had a
15 wonderful result with one side effect being constipation to
16 the point of the emergency room, as Dr. Pena had talked
17 about earlier.

18 We went through many, many different things to
19 get to that point, starting at school age being
20 embarrassed, humiliated, segregated away from the other
21 ones because of her drooling, coming home with wet artwork
22 from excessive drooling. We call it the river.

23 She's very, very cognitively aware, 10 years
24 old, in fourth grade, mainstreamed, in LD classes as well.
25 She has a full-time paraprofessional who does a lot of

1 | observing, but yet we try to give her independence.
2 | Through independence, the head is hung down. Drooling is
3 | more excessive. Her natural positioning is this. So, it's
4 | a constant reminder all day long of head up, swallow. It's
5 | just not the natural reflex that we do have.

6 | At one point someone in here earlier had talked
7 | about the convenience of we look at as drooling. I went
8 | through that. I went to an oral surgeon seeking help to do
9 | something about the drooling. They were going to do the
10 | surgery with removing the glands here because leaning
11 | forward all the time, those two were just consistent
12 | rivers, and then reverting the other two down the throat so
13 | she didn't get dry. She began to cry when they approached
14 | her to do the orral examination. He was wonderful. But I
15 | started to cry, and I thought am I doing this because it's
16 | really necessary or is it convenient to me not to deal with
17 | the problem.

18 | So, she's very, very cognitive. I said, what
19 | is Mom doing here? And she said, I don't know. And I
20 | said, is it bothering you? No, it isn't. At that point I
21 | realized until it becomes a bother to her, even with the
22 | cruelty of society, I did not have the right to make that
23 | decision.

24 | So, we furthered on in, and she got to the
25 | point to where through different things that we would use

1 to help contain the drool so it did not get to the chest,
2 she was called a cowgirl and many other names, and she
3 would come home emotional. It was very hard to modify
4 something that wasn't noticeable around her chest area.

5 She was sick very often, on antibiotics
6 sometimes twice monthly, used a nebulizer regularly.

7 We started Robinul last May. We have not used
8 the nebulizer one time. It has been completely excluded.
9 It still sits in the closet. She has been on approximately
10 three bottles of antibiotic. She still has enough saliva
11 that the chin is still a little wet, but there's none of
12 the drip to the chest. So, exposure to weather is not as
13 critical and so forth.

14 Dr. Pena, on first meeting her, she was
15 wonderful. She asked more questions directly to Ronny-Kay
16 and her team of doctors did rather than myself, which I was
17 very impressed with. She answered all of them. When asked
18 to approach her mouth, she was ready at this time to get
19 rid of the problem because she wanted to be accepted by
20 society.

21 So, they did an oral examination and they
22 discussed their medical language, and we tried to
23 understand it. Then they said, we feel she's a good
24 candidate.

25 At that point, she was put on the Robinul with

1 me understanding some of the side effects and so forth, and
2 that if I had any problems to call the office. And I did
3 frequently, and they were extremely supportive. I was
4 concerned about less urination. We were very active going
5 to King's Dominion. I was afraid she wasn't going to
6 sweat, so I called constantly. Is this going to be a
7 problem? She was very thorough, very patient. Increase
8 your liquids, et cetera, et cetera.

9 So, we really did not have any side effects.
10 Pupils did dilate, a little bit of stomach cramping in the
11 beginning. Fortunately, she can communicate and feed back
12 the way she feels entirely if it's an earache, whatever.
13 So, there was a little bit of complications with the
14 stomach.

15 Once we got regulated, I think it was great.
16 She loved it. Last year she graduated from speech therapy,
17 which is a very big step. Normally we never expected her.
18 And the focus in there was massaging tools. And we
19 through an ice cream party for the graduation. It was
20 important. It's just been very, very successful.

21 At this point the only thing that I find a
22 bother -- it doesn't her. She can still focus on
23 everything. Nothing impairs her as far as the medication,
24 but constipation was in a very, very bad state. She had
25 become dependent upon enemas, not me realizing that it was

1 due to the medication. Finally, she actually said, Mom, I
2 need to go the emergency room. I'm in great pain. I just
3 don't see everything, even though I try to make
4 observations.

5 So, on our second one, it came to me. Oh, my
6 goodness. All the secretions in the body are being
7 decreased here, so this is probably the issue.

8 The doctor did not take it upon herself to
9 investigate the medications I had listed, which Robinul is
10 all that she takes. There are no seizure activity or
11 anything with Ronny-Kay. She called the pharmacist to get
12 a feedback on the medication. Of course, there was a
13 higher risk than many other medications for constipation.

14 At the second time, it was digitally removed
15 once again. Throughout this time period, she realized the
16 significance of stool softener and being able to swallow.
17 So, she graduated to the swallowing of the pill. Thank
18 goodness.

19 So, we had to just exclude the Robinul, get the
20 body regulated, get it hydrated, and now we are back again
21 using Robinul to a smaller amount in the beginning with
22 stool softener and a little bit of fiber increase and fluid
23 intake increase. And hopefully that will regulate it all.

24 Other than that one default, this medicine is
25 like heaven to me simply because it made such a difference

1 | in her self-esteem, her ability to feel comfortable in a
2 | large group setting which she felt and knew that it did
3 | draw attention and the kinds could be very ugly. Because
4 | of her head control, that was one of the biggest things to
5 | me. Her sicknesses that were so consistent and anything
6 | she does, she has fluctuating tone. But when she tries to
7 | anything with the hand -- she is right-handed -- the head
8 | has to watch the hand. Therefore, the head, once again, is
9 | consistently staying in this down position, which is where
10 | most of her work stays and everything, which was being
11 | destroyed.

12 | So, on a personal level for our experience, it
13 | has been a wonderful medication with some side effects, of
14 | course, and that's over a year's duration, from last May
15 | coming up to this one. She has been very happy with it.

16 | The physical, occupation, and para at the
17 | school have all done observations as well, kept notes.
18 | Through sicknesses her drooling was more excessive, and
19 | Robinul did not decrease that. We didn't increase it
20 | during that time either. It's been very gradual to build
21 | up to where we're at now with Dr. Pena with lots of
22 | questions and observation. It just wasn't going right into
23 | it. At first I could hardly even tell that the medication
24 | was working, and I'd call and say, well, what am I supposed
25 | to expect here? It takes a little time. It must build up

1 gradually and slowly so the body can adjust to a new intake
2 of medication.

3 But if you have any questions on something I'm
4 missing, because I am extremely nervous, please ask and I
5 will answer the question.

6 DR. CHESNEY: You've done a terrific job, very
7 descriptive. You raised all the issues that we've been
8 talking about, but it makes much more of an effect when you
9 talk about it.

10 I think what I'd like to do is hold the
11 questions for Drs. Stiefel and Goldstein until after the
12 break, but does anybody have questions for Ronny-Kay's
13 mother? Dr. Nelson.

14 DR. NELSON: How often do you need to use the
15 medication, and do you find the administration difficult,
16 disruptive to daily routine?

17 MS. HURLBURT: I did at first simply because I
18 had to crush the pill. If we were out and about -- and we
19 are very active -- I would have to find somewhere to get
20 ice cream, apple sauce, something, do a mixture. It was a
21 very big inconvenience. Once again, graduation to
22 swallowing of a pill has been wonderful, just water.

23 Right now we're doing it twice a day, one
24 before school with breakfast, 2 milligrams, 2 milligrams
25 after school when returning home. I don't see on our

1 | personal behalf a significant change that she starts
2 | drooling excessively before the second dose comes in. It's
3 | pretty consistent to be maintained all day by those two
4 | doses.

5 | DR. CHESNEY: Dr. Szeffler.

6 | DR. SZEFLER: Once again, you did very well.
7 | It is not easy to talk in front of big audiences if you
8 | haven't done it a lot.

9 | MS. HURLBURT: Yes.

10 | DR. SZEFLER: What are your personal
11 | experiences in terms of the formulation, things like taste?
12 | When you had to use the other formulation, was it a problem
13 | in terms of pharmacies, inconvenience in terms of time,
14 | additional cost, delays, anything like that that you ran
15 | into?

16 | MS. HURLBURT: She does have a very strong
17 | sensitivity to textures in food, medications. I had a
18 | granulator. When I did do that, it was beady. She has a
19 | gag reflex. It has gotten better. It was a big
20 | inconvenience, very much, simply because if we were out,
21 | especially if it was a windy day, I was concerned with the
22 | chest being wet. That was our initial search out for help
23 | anyway. If we did not have it with us, wasn't expecting to
24 | be out that long -- usually you're prepared when you have a
25 | child with special needs -- we would have to find somewhere

1 to get something on the soft side to mix this to take away
2 the taste and the texture, apple sauce, ice cream,
3 whatever. It had to be something. Through desperation, we
4 could get a candy bar with caramel, anything to disguise
5 the texture and taste. And it was very inconvenient.

6 Now, with swallowing the pill, which has been
7 great for self-esteem and independence, feeling that she's
8 taking control of things, it has been much better.

9 DR. SZEFLER: Is taste a problem? Is it like a
10 bitter taste or after-taste?

11 MS. HURLBURT: I asked her that and she's very,
12 very capable to respond. She says it's like if I were to
13 take an aspirin. It's bitter. It's yucky.

14 DR. SZEFLER: Just a couple other questions to
15 follow up on that. Have you noticed anything as apparent
16 in terms of dosing strategies, when to give it, when it has
17 it's most effect, when it's best for you and her in terms
18 of family circumstances, before meals, after meals,
19 nighttime?

20 MS. HURLBURT: I do try to give it with a meal.
21 Not that we've had any trouble with it being given on an
22 empty stomach. It just makes me feel a little bit better
23 that it is going in with -- never have I heard or read
24 through research that it is affected or has more of a
25 benefit on an empty stomach.

1 As far as an inconvenience to the family and so
2 forth, it has not been because I do have two older children
3 who are very involved with Ronny-Kay's well-being and
4 caretaking. They're typical siblings, arguments, so forth.
5 But we've all kind of grown into there are certain things
6 that we are willing to give up and change and modify to
7 benefit her as being a part of our family.

8 So, I don't know if I answered that entirely.

9 DR. CHESNEY: Dr. Edwards.

10 DR. EDWARDS: In terms of using the measurement
11 tools that Dr. Pena has given you in terms of measuring
12 secretions and also using it in school, how easy has that
13 been to do? And also how easy has that been to get the
14 people at school to do this as well?

15 MS. HURLBURT: It was actually very successful.
16 The only disadvantage was that we had a new therapist come
17 in who wasn't familiar with her history. The longer you're
18 with a patient or a child, the more you learn them, and you
19 know the drool before the medication was intervened and
20 then to now.

21 As far as her paraprofessional, she was
22 wonderful. She's with her all day. So, she could do just
23 a drool chart on 15- and 30-minute intervals, and she would
24 just take note. At different times, there was more
25 drooling prominent, such as things that if Ronny-Kay was

1 | doing anything that consisted of her head needed to be up
2 | to pay attention to what was going on, not that there was
3 | lip closure, but there was just less probability for the
4 | drool. But any other times, during art activities or
5 | anything she had to work with the hand, the head was down.
6 | So, they could do a record of all of that.

7 | There was points about mid-morning, about 2 to
8 | 2-and-a-half hours after the medication was the highest
9 | peak of maximum result I guess you would call it. It was
10 | actually last towards the afternoon, and then the drooling
11 | starting to come back not near as profuse as one point but
12 | ready for the next dose when she got home.

13 | To answer your question, it wasn't difficult
14 | and there was no apprehension to the people that worked
15 | with her to evaluate and take note for me.

16 | DR. CHESNEY: Dr. Walters.

17 | DR. WALTERS: This is not at all a medical
18 | question, but I'm concerned about the cruelty of
19 | classmates. I'm just wondering if there's anything that
20 | you think could be done by the school or by the treating
21 | physicians or anyone else to educate those very intolerant
22 | classmates.

23 | MS. HURLBURT: I think it's a big importance,
24 | and especially because she is very cognitive. It's very
25 | hard for me not to get emotional because they have been

1 | cruel. A lot of people automatically assume retardation
2 | because of the dropped head and the drooling. As soon as
3 | her head is lifted and they see here and the drool begins,
4 | some people want to turn away. They want to think that she
5 | is automatically retarded, which is very sad.

6 | What I did on a personal level, because kids
7 | were so questioning of it, sometimes not even due to the
8 | drooling, but why do you have tissues tucked in your shirt?
9 | At a younger age, it was more of an inquiry. As they got
10 | older, it was that they couldn't stand it. It was gross.

11 | And I think at one point Ronny-Kay herself did
12 | not know how to answer why are you drooling. She was just,
13 | Mom, tell them. She didn't know what to say.

14 | There is a group that was called New Kids on
15 | the Block. It's puppets who have different disabilities.
16 | I had requested through our principal that she bring them
17 | in during disability awareness. They broke it down into
18 | smaller groups in the elementary school, K through 2nd and
19 | 3rd and 4th and 5th and so on, and did a skit kind of
20 | portraying who the person was. They asked me details about
21 | what I wanted to focus on, and I said drooling, why am I in
22 | this chair, et cetera, et cetera, and other diagnoses
23 | within the school as well.

24 | Then they gave a free forum for the kids to ask
25 | any questions. And our hopes was for them to ask, why do

1 | you drool? How come you can't control it? Why do you wear
2 | this? It was successful, but still you're going to have
3 | the kids who -- just out of the attention that a child like
4 | Ronny-Kay seems to ooze out of people, from her disposition
5 | being so wonderful, it's a jealousy issue more so than not
6 | understanding or compassion, if that makes sense.

7 | DR. CHESNEY: Great answer.

8 | One last question. Dr. Kelsey.

9 | DR. KELSEY: Thank you and your daughter for
10 | coming today, Ms. Hurlburt.

11 | I wanted to follow up on what Dr. Edwards was
12 | talking about. Can you or can your daughter discern from
13 | day to day differences in how effective the medication is?
14 | Are there some days when it seems to work well and others
15 | it doesn't so much?

16 | MS. HURLBURT: Sometimes, yes. Fortunately,
17 | like I said, we've not had as many sicknesses. The saliva
18 | is always decreased, the production, but not entirely. But
19 | there are days when she has been sick that, yes, there is
20 | more. And I know it's not producing more. I don't know if
21 | it's just that at times she's also swallowing because we're
22 | still reminding her of that. It's not like we give up the
23 | field of let's try to do this independently without
24 | medication. So, it's a constant reminder of swallowing,
25 | lip closure. We've even got the siblings in the home

1 making habits to squeeze her face up for a kiss to
2 constantly stimulate the facial muscles. But it does seem
3 at times -- and I don't know medically how to answer that
4 -- that there is more drooling than at other times.

5 DR. KELSEY: So, if you had something other
6 than the pill that you give twice a day, you could give a
7 little bit more in a situation like that. That would be a
8 possibility.

9 MS. HURLBURT: Oh, most definitely if given the
10 opportunity. As far as I would feel comfortable to
11 evaluate?

12 DR. KELSEY: Yes.

13 MS. HURLBURT: Yes, because I do spend that
14 much time with her and I do that much assessment with her
15 from loving her, that whatever makes her comfortable -- and
16 this was by her choice this time to see Dr. Pena. I would
17 feel comfortable, yes.

18 DR. KELSEY: Thank you.

19 DR. CHESNEY: Ronny-Kay, thank you. I didn't
20 mean to startle you.

21 (Laughter.)

22 MS. HURLBURT: She asked if she could speak
23 here today.

24 DR. CHESNEY: Thank you very, very much for
25 coming. Do you want to talk to us?

1 RONNY-KAY: Yes.

2 DR. CHESNEY: Great.

3 RONNY-KAY: Well, as you guys know, I am here
4 today with my mother. Of course, this is about my
5 drooling. I think my drooling is okay except when kids
6 laugh at me.

7 MS. HURLBURT: So, that's why we're here.
8 Right? And you're on the medication.

9 Say, that's it for today.

10 RONNY-KAY: That's it for today. Thank you.

11 (Applause.)

12 DR. CHESNEY: Thank you both again for coming.
13 I know it was hot outside and it's awkward getting here.
14 We really appreciate it.

15 MS. HURLBURT: It was a privilege.

16 DR. CHESNEY: Could we take a break just for 10
17 minutes instead of the 15 minutes and, according to that
18 clock, be back no later than 10 to 11:00?

19 (Recess.)

20 DR. CHESNEY: Before we ask questions of Dr.
21 Stiefel and Dr. Goldstein, we are scheduled for an open
22 public hearing. There's nobody who has indicated that they
23 wanted to speak. Is there anybody here who did want to
24 speak but hadn't let us know?

25 (No response.)

1 DR. CHESNEY: Let me ask the committee then if
2 you have any questions for Dr. Stiefel or Dr. Goldstein.
3 Dr. Kauffman.

4 DR. KAUFFMAN: Maybe some of the other experts
5 can comment on this too, but I gleaned the impression this
6 morning from both some of the presentations, as well as the
7 last presentation, although there is a long laundry list of
8 potential side effects from the anticholinergic, that the
9 one that really is most problematic is the constipation, GI
10 problems. Is that a true perception? Because that seems
11 to me to be somewhat manageable with osmotic and bulk
12 laxatives and stool softeners, et cetera.

13 But some of the other side effects that I would
14 have anticipated, but didn't hear about, would be
15 intermittent difficulty with vision in school trying to
16 focus on reading or artwork because of the effects on the
17 eye, urinary retention, and possibly some intermittent
18 tachycardia or temperature control in hot weather and those
19 kinds of things. Are those really negligible or do they
20 pop up also?

21 DR. STIEFEL: May I address that? Again, that
22 was a very quick pass through that slide. Our experience
23 is different than other folks. I think the difference in
24 our experience is that we are just more involved in the
25 global management of the overall health care needs of the

1 child.

2 We were just also talking about that over the
3 break that a lot of these side effects take a long time to
4 recognize that they're even a problem. We find the
5 temperature regulation problems particularly in the summers
6 where the hydration issue is a major issue. Actually we've
7 hospitalized many kids over the years that have just gotten
8 severely dehydrated, other sorts of issues. Constipation
9 is manageable but it is a significant management issue in
10 these children.

11 We find the accommodation problems and the
12 other things that you're talking about as sometimes a
13 problem, but it's very individualized. There have been a
14 couple of kids that have complained of it, but it's not
15 been over all.

16 We do find problems with the central nervous
17 system that I think are minimized. The problem is how do
18 you assess it. I think the reason we don't talk about
19 these things is because we don't really know how to both
20 quantify and assess those things. These kids many times
21 have behavior problems and sometimes very severe behavior
22 problems.

23 Again, it's just sort of that one other
24 addition to sorting this out. But as we sort out, as we
25 remove kids -- 95 percent of our work is removing kids from

1 the psychopharmacology that is inappropriate and sort of
2 starting over again -- we find out and we are able to sort
3 these things. It's not something, though, that comes out
4 right away. Again, there is the actual cycle itself and
5 then there's the period of time in terms of recognition of
6 those side effects. And that changes over time also and it
7 changes by season. It changes by a lot of other things.

8 So, I think they're there. I just don't think
9 we do a good job of looking at them and recognizing them,
10 particularly in the time that we do in terms of traditional
11 medication studies.

12 We also have come full circle to realize that
13 in the studies that we're looking at, we probably can't do
14 randomized controlled trials, to address your issues a
15 little bit earlier -- but I am going to expand on it --
16 because there is such a strong physiological effect of this
17 medication that it never is blinded.

18 These are lifetime medications. I didn't make
19 this point, but if a kid responds to this, they're going to
20 be on this the rest of their life. There are many
21 families, when you approach it from that perspective, that
22 will tolerate AB/AB trials to be able to actually look so
23 you can over time begin to sort out the side effect profile
24 and other sorts of things. That's where we are moving
25 towards with not only this medication, but many of the

1 medications in kids with disabilities, AB/AB trials
2 because, again, it's a commitment lifelong. Even the kids
3 themselves and the adults are willing to go through that
4 many times. But it's again how you present the package of
5 information and how you make the argument.

6 DR. KAUFFMAN: And the baseline is stable
7 enough that you can do AB/AB?

8 DR. STIEFEL: Ask me in two years, Ralph. You
9 know we're a new shop.

10 DR. CHESNEY: Dr. Goldstein.

11 DR. GOLDSTEIN: We have another variable in
12 play. Again, these children have multiple disabilities.
13 Parents are desperate for interventions. And there is a
14 world of interventions out there. Hyperbaric oxygen
15 therapy, et cetera, et cetera, conductive education, all
16 kinds of things. I'm not denigrating any of them. But
17 parents will seek these out, particularly now on the
18 Internet. And the variable comes into a study that it's
19 difficult to prevent them from seeking out this other
20 intervention in addition to. So, it makes the analysis of
21 the data extraordinarily difficult because how does
22 hyperbaric oxygen impact upon anticholinergic medication?
23 Nobody really knows. We know it has an effect on GABA
24 reduction. We're fairly certain of that.

25 So, I just bring up the issue again of why the

1 size of the denominator has got to be as large as one can
2 possibly achieve because of these other variables that are
3 going to be introduced, and you can't tell a parent, no,
4 your child cannot have conductive education.

5 DR. STIEFEL: It didn't come up and it's
6 interesting that alternative and complementary care and the
7 Internet didn't come up in this discussion. Again, I think
8 families do come to us, in the long-term relationship, for
9 guidance to what to pay attention to and to what not to pay
10 attention to. That's increasingly become a major part of
11 our work, helping families sort these things out.

12 The point again is these studies only work if
13 you have a long-term relationship with them to be able to
14 make those kind of studies work. Part of that is the
15 partnership to be able to address issues such as that.

16 Again, some of the alternative and
17 complementary medicines that are being put in these kids
18 also have anticholinergic effects. It wasn't addressed but
19 it's part of the polypharmacy issue that I addressed.

20 DR. CHESNEY: I have a question about two side
21 effects that haven't been discussed. You were the only one
22 who brought up the thickened pulmonary secretions, which I
23 was concerned about, and the tachycardia. If we were to
24 look at those, it would take a much more aggressive
25 approach than the constipation and things that we can see.

1 Are those significant enough? I also think it would be
2 very hard for children to articulate palpitations and
3 tachycardia. I don't know how hard it is to know that.

4 DR. STIEFEL: With all that's going on with
5 anticholinergic and QTC and all the other sort of things in
6 terms of the many indications, we haven't had it be a
7 significant problem. The literature mainly focuses on kids
8 with Down's syndrome and tachycardia, and there seems to be
9 some implication that those kids are more sensitive,
10 although I don't think the science is good enough to really
11 say that at this point.

12 We haven't seen it be an issue other than with
13 kids who are sort of on the borderline, have QTCs floating
14 in the 440 range, somewhere down the road, and then we just
15 push limits a little bit more. Some of the kids also that
16 we see -- again, it comes back to the complexity issue --
17 have complex congenital heart disease when you're seeing
18 kids with genetic syndromes.

19 So, we haven't run into it, but I think it's
20 going to be an issue. It's just going to be like what
21 we're involved with with Mellaril right now and some of the
22 other drugs in regards to these kind of things. Eventually
23 there probably would be something that over time adverse
24 things would be reported. There probably would be
25 problems, and retrospectively we would then come back to it

1 and revisit that. "But I haven't had it be a major problem.
2 I haven't had to discontinue with any in our study, and I
3 don't know if you have with your study.

4 DR. PENA: So far, except for the one patient
5 who had the tracheal secretions that were causing the
6 obstruction, I haven't had to discontinue. As a matter of
7 fact, when I titrated it down, it improved. That's the
8 only really adverse outcome I would say that I've had.

9 DR. STIEFEL: On the other hand, regarding the
10 pulmonary stuff, it just depends on the complexity and all
11 the factors that go in, the posterior drooling component
12 and all the other things that go into very complex
13 management of these kids who have neonatal histories, spent
14 three years in the BPD units and come out vent dependent.
15 If we are honest with ourselves about trying to sort out
16 what these medications are really doing and how they're
17 going into that vicious cycle, it's very, very difficult to
18 sort out.

19 DR. CHESNEY: Thank you.

20 Other questions? Dr. Fink.

21 DR. FINK: Just a comment. On the pulmonary
22 issues I think the vast majority of children with lung
23 disease, if you effectively decrease their drooling, you
24 also decrease the posterior drooling and aspiration. The
25 majority of them actually do better on these drugs so that

1 pulmonary complications are down, viral infections decrease
2 because most respiratory viruses we now know are aspirated
3 into the lung. So, overall the pulmonary status usually
4 improves and it's a rare patient inspissates.

5 DR. STIEFEL: And if you don't dry them up
6 completely, it comes to the titration. If you're in that
7 balance, you don't get into problems. That's been our
8 experience also. But it has to be the careful titration
9 that gets you to that point.

10 DR. CHESNEY: Dr. Nelson.

11 DR. NELSON: I'd like to just make an
12 observation and get some reality testing, I guess, in terms
13 of what I'm hearing.

14 Complexity is a major theme of all this, and
15 variability in terms of physiologic response to the
16 medications, variability in terms of the value of a range
17 of efficacy and adverse event balancing that would occur
18 both on the part of any given child and on the part of any
19 given caregiver for that child, to parent, to foster
20 parent, to institution, et cetera.

21 So, in a sense, the clinical management that
22 involves a titration of a dose to an outcome that balances
23 both the child's physiologic response and the outcome
24 values, if you will, of the caregivers is how you're
25 managing this situation.

1 So, then I ask myself what are we going to try
2 and accomplish in the FDA process, drug development, study
3 design, and that sort of thing. It strikes me you'd end up
4 with a very complex study, and it's not clear to me, as
5 long as you have validated measurement tools -- and
6 frankly, you've got a pretty good list of tools compared to
7 even the pain management area.

8 I guess my question is, is it really a question
9 of how you approach the titration and outcome? It seems
10 that good clinicians have a handle on that. Or is it
11 really a question of formulation, having some different
12 tools, if you will, to put into that kind of setting?
13 What's really the major issue here? Is it just getting a
14 better preparation and formulation?

15 As I think about the transdermal preparations,
16 if you can't come up with a predictable dose response, you
17 can't titrate a patch very easily as opposed to titrating
18 pills or liquid preparations or other formulations. So,
19 the formulation may be somewhat constrained by the ability
20 to establish a set dose if that dose is going to vary
21 patient to patient based on the complexities that you've
22 been describing.

23 I guess I'm asking for some guidance about what
24 you really see is the key issue here. Is it really the
25 dose response study kind of issue, or is it that we just

1 need to have some better formulations to begin to provide
2 management tools that you need?

3 DR. STIEFEL: Does somebody else want to answer
4 that question? Because that is the question.

5 I'll give you an opinion. A lot of it depends
6 where you folks are at as you approach not only drug
7 studies in children but drug studies in special needs
8 populations in children. It comes back to that paradigm
9 shift that we were talking about earlier. You can either
10 do business as usual and just address those basic issues,
11 or you can also take an education responsibility and you
12 can push the paradigm, depending upon how far that's
13 pushed. I don't know, and that's again none of my
14 business.

15 But even if you, though, do the things that
16 you're talking about, those things initially will be
17 extraordinarily meaningful, the formulation questions.
18 Again, if you look at almost all drugs that come out, this
19 is one place where we have to be proactive in terms of
20 titration schedule and education, folks.

21 Let me use an example away from this, but
22 lamotrigine, which is an anti-epileptic drug which we
23 titrated too fast and created Stevens-Johnson syndrome in a
24 lot of kids. If you look at the history of things,
25 titration, knowledge and wisdom always come out

1 retrospectively after initial FDA in the post-marketing
2 trials. This is one place where you're going to hurt kids
3 and families, though, if we don't do this prospectively and
4 at least have good guidance in regards to these things and
5 formulations that are able to be used in a way, as you've
6 talked about, through a broad dosage range.

7 However, when we talk about broad dosage range,
8 we are not talking about an infinite dosage range. We are
9 talking about a broad dosage range. And certainly there
10 will have to be response to that from the private sector,
11 but it's not undefinable. There is a dosage range that we
12 use. Again, has that been defined? No. But it's not
13 infinite.

14 I could continue to comment all day long, but
15 to at least address those two issues.

16 DR. CHESNEY: Dr. Szeffler.

17 DR. GOLDSTEIN: While they're adjusting that,
18 let me just also say I think the model is insulin therapy
19 for the diabetic in that one is titrating nearly on a daily
20 basis for the severe diabetic, for child diabetes. One
21 isn't doing blood levels as endpoints. One is looking at
22 blood glucose levels which are some indicator of something,
23 but many of us aren't quite sure what. So, we're dealing
24 in this type of paradigm where the endpoint here is the
25 amount of drooling, but what we do have is this horrible

1 upper motor neuron lesion which is affecting tongue
2 mobility, tongue motility, pharyngeal motility, and in each
3 child and in each subject, that is somewhat different. So,
4 again, it's this issue of in that particular child with
5 that particular combination of neurological lesions, the
6 only measurement tool that you've got effective at the
7 moment is the degree of drooling and how are they handling
8 their sputum.

9 DR. NELSON: I agree with what you've said, but
10 let me just make one observation. The difference I think
11 in this context from diabetes is we can all agree that you
12 should have a blood sugar of X. What you want to do to get
13 there, how many times you want to take your insulin, and
14 all that kind of thing may vary as far as lifestyle issues.
15 Correct me if I'm wrong. You have an overlap of efficacy
16 and adverse events precisely in the dosage range that
17 you're going to be working with potentially to where the
18 outcome itself that each individual child and parent would
19 accept is going to vary in a way that's very different than
20 the insulin example.

21 DR. GOLDSTEIN: That's correct.

22 DR. NELSON: So, you're not only changing the
23 dose you might need. Everybody responds differently to
24 insulin. But you're changing the actual outcome
25 measurement at the same time, which is what makes it

1 particularly complex.

2 DR. GOLDSTEIN: Yes, because we don't have an
3 objective endpoint, i.e., blood glucose levels, that we can
4 be comfortable with in terms of saying this is a range of
5 blood glucose levels which we will accept. Here what we're
6 saying is here is the range of salivation which is a very
7 imprecise measurement at the extreme. So, we are balancing
8 the adverse effect of cutting down on salivation against
9 what is acceptable social impact of drooling.

10 My daughter is a juvenile diabetic and checks
11 her blood glucose levels six times a day. She's an adult
12 now. She's accepted this. She knows how to handle it
13 reasonably well. But her protocol of therapy is very
14 different from somebody else's who is also a juvenile
15 diabetic. The best we could do was educate her to the
16 range and to certain endpoints that she's got to be
17 sensitive to as a young adult. That's the only reason for
18 my analogy. It's not a dose effect because a certain
19 amount of insulin at 2:00 in the afternoon will have a very
20 different effect than before she goes to bed.

21 DR. CHESNEY: Dr. Szeffler.

22 DR. SZEFLER: I just wanted to follow up on two
23 points, one that Dr. Chesney made and another one Dr.
24 Nelson made in terms of this formulation. I think what
25 we're trying to grasp from you is I think we've got a

1 situation where there's a drug that's helpful, but it's
2 problematic in terms of what we think is a narrow range
3 between beneficial and adverse effects. It would seem to
4 me, in hearing the discussions, that you have a product
5 that was developed for something, used for something, I
6 think for acute secretions, although I don't think it's
7 indicated for that, but now you're using it for continuous
8 secretions. It would seem logical to me, to follow up on
9 Dr. Chesney's point, that maybe a recommendation in the
10 formulation development like a sustained release product
11 might help.

12 But what I don't have a good feel for is the
13 percentage of patients who are likely to respond and if the
14 effect on secretions is one of the first indicators. I
15 sense what happens is that if somebody doesn't get a
16 response, then they escalate the dose, and when they
17 escalate the dose, they kind of get a high peak. And then
18 you're going to run into crossing that threshold where a
19 higher proportion of patients may get the adverse effects.

20 Do you think making a recommendation to
21 investigate the formulation of a sustained release
22 preparation would add something to your pharmacopeia that
23 would make it more convenient, reduce the problems with
24 taste, and maybe make an effective preparation for this
25 target population rather than taking the next

1 | extemporaneous preparation and using it in areas that may
2 | create jeopardy because of misuse?

3 | DR. GOLDSTEIN: The answer to both questions is
4 | yes. We're going to find in this heterogeneous population
5 | a population of children for whom a sustained release
6 | medication will serve its needs quite adequately and not at
7 | the moment worrying about the titration issue. We're going
8 | to find another population which is so unstable, in terms
9 | of its activities of daily living, that sustained release
10 | might be extremely dangerous.

11 | So, again, if I might use my insulin example, I
12 | think we haven't defined that population and we will need
13 | to define it, which is why these studies will have many
14 | beneficial side effects in terms of information and data
15 | about the characteristics of this population.

16 | DR. CHESNEY: Dr. Stiefel, you were going to
17 | respond.

18 | DR. STIEFEL: Again, it's a heterogeneous
19 | group. There are going to need to be multiple
20 | formulations, not only sustained release, probably a
21 | transdermal system also, perhaps even looking at new and
22 | novel delivery mechanisms in terms of looking at the
23 | pharmacokinetics and absorption through, again, many of the
24 | other things that are looked at. I don't think there's
25 | going to be one answer for everybody. Obviously, you just

1 | heard that from the most important source, that for this
2 | young woman, learning how to swallow a pill was a great
3 | thing, but that doesn't work for everybody. So, we're
4 | going to need a range of things. I think using examples
5 | such as clonidine or stimulants or any of the other things
6 | that we use that need a broad titration range, you're going
7 | to need multiple different types of products to address
8 | this over time, and one thing will not fit for all.

9 | DR. CHESNEY: Dr. Fink.

10 | DR. FINK: It strikes me that this is primarily
11 | a formulation problem but not exclusively one. Obviously,
12 | long-term time-released products are one approach. The
13 | other one that sitting here just fascinates me is what
14 | about the use of a reditab where you dissolve it on the
15 | tongue and you might even get more activity at the site
16 | where you want activity very quickly and you don't even
17 | have a swallowing problem. So, looking at something like a
18 | reditab formulation where it dissolves and you don't have
19 | to swallow a pill might enhance both efficacy and
20 | convenience of treatment.

21 | DR. STIEFEL: We would encourage novel delivery
22 | and formulation.

23 | DR. CHESNEY: That's great. Why is it called
24 | reditab? Is it at the ready?

25 | DR. FINK: Well, Claritin is out in that now

1 | where it literally "dissolves on the tongue in 2 to 3
2 | seconds and you can swallow the liquid, but very rapidly
3 | dissolved on the tongue and it's sort of a soft tablet that
4 | doesn't require swallowing.

5 | DR. CHESNEY: That's great.

6 | DR. SPIELBERG: A question for FDA because
7 | formulations don't grow on trees. You need sponsors to do
8 | this.

9 | There are two questions. One is current
10 | exclusivity and patent status of the compounds we're
11 | talking about. And two, do we really want to develop any
12 | of these old dogs, or do we want a better drug?

13 | Those are the two critical things because if
14 | we're going to go forward and really solve the issue and
15 | come up with something that actually is going to be both
16 | user friendly for the kids and for the parents and
17 | pharmacologically appropriate, we have to deal with are we
18 | happy with the current spectrum of activities and targets
19 | associated with the current compounds available. What is
20 | the status of all of those compounds? Who owns them and
21 | who is going to do it if we are going to go after old
22 | compounds? Or are we really talking about discovery here?

23 | DR. KELSEY: Well, you're absolutely right that
24 | we're at the mercy of the sponsors. FDA reviews what is
25 | brought to us. We're very early in the process with this

1 particular indication and that, combined with the fact that
2 we have limited knowledge about this patient population and
3 studying any kinds of drugs in this group, FDA as well as
4 the division, we've come to you all to publicize it and to
5 get your guidance.

6 The antimuscarinics that Dr. Mathis talked
7 about are, of course, have been around for a long time. I
8 can't tell you about what specific patent life any of them
9 may have left, and the issues about use patents and all
10 that sort of thing get very complex. I'm certainly not an
11 expert on it.

12 DR. SPIELBERG: That is a fairly key point,
13 though, in terms of whether FDAMA is or is not a mechanism
14 for these compounds because whether there are incentives
15 around still or whether we need another mechanism for
16 driving it for this particular class of drugs really is
17 critical in terms of our understanding.

18 DR. KELSEY: Yes, sure. That, of course, goes
19 way beyond our level at the review division as far as what
20 FDA's policy is going to be. That's really a legislative
21 issue, what sorts of additional incentives Congress might
22 give for this sort of thing. We review what comes in, but
23 I think that this type of a forum can stimulate sponsors to
24 at least think about different things. We don't have patch
25 formulations. We don't have sustained release or reditabs

1 and that sort of thing. I'm sure that people could get
2 additional patent life there.

3 Of course, there is nothing approved for the
4 indication of drooling. I think I might have misspoken
5 earlier when Dr. Fink asked a question. This is not
6 approved for drooling in adults or children, of course.
7 So, I think that there are some opportunities there for
8 industry to develop these compounds.

9 DR. SPIELBERG: The latter point is critical,
10 though. If they're not approved for drooling, you need a
11 clinical efficacy program. There's no way around that.
12 It's not just a formulation issue. It's a new indication.
13 So, whether it be a better chemical entity or whether it be
14 a redefining of one of the older drugs, it's a real
15 development program.

16 DR. CHESNEY: Dr. Nelson, did you still have a
17 question?

18 DR. NELSON: No. I was just pointing to Steve.

19 DR. CHESNEY: Dr. Walters.

20 DR. WALTERS: I'm trying to think about a
21 design that would work with the drugs that are currently
22 available, and the only analogy I can think of at the
23 moment is from a very different field. There was a cardiac
24 arrhythmia suppression trial that involved multiple drugs
25 and a titration phase that was tailored to each particular

1 patient. So, the simplest design that I can think of would
2 be a head-to-head comparison of two or three of the best
3 existing drugs with the titration phase at the beginning
4 and then a large enough sample size that one could have
5 some confidence in the result.

6 So, Judith, you're an expert on this kind of
7 issue.

8 DR. O'FALLON: I think this is an ideal
9 situation for doing your AB/AB or ABC/ABC/ABC type study.
10 Probably AB/AB is better.

11 But he was talking about doing a crossover
12 study. There was one in our packet, a 1989 study, that
13 really I thought was extremely well designed, had a
14 terrible time with the analysis folks. They couldn't
15 figure out what they found. But the design would be a
16 model. They had a baseline. Then they had a treatment
17 period. In this case it was a 2-week. I don't know. You
18 would have to talk the issues. But there was a week of
19 titration and then a week of, I call it, cruising altitude.
20 Then they went to a washout period, and then the second
21 drug, or in this case placebo, and again a week of
22 titration, a week of cruising altitude. Then they compared
23 the results in the second weeks between the two.

24 I think in this kind of a disease where the
25 drooling goes right back to as bad as it was as soon as you

1 | remove the therapy," this is a perfect example of a
2 | situation in which that would work.

3 | Now, that doesn't answer the question of long
4 | term. It will address does it affect the drooling. Is it
5 | efficacious in drying off the mouth and short-term
6 | toxicities.

7 | If you're going to do long term -- and I think
8 | you have to from everything I'm hearing -- then you
9 | probably have to roll over into a continuation study, which
10 | is another very well adapted thing where they would choose
11 | one, maybe even still be blinded. Who knows?

12 | These would, I think, need to be blinded
13 | because the one piece of information that I could get out
14 | of that '89 study, as far as I could see, was that there
15 | was a placebo effect. My own experience with blinded
16 | treatments in things like pain, hot flashes, and so on,
17 | having done a number of these studies, there is a placebo
18 | effect. At the beginning, everybody is optimistic and it
19 | just happens. So, you have to be able to sort out the
20 | placebo effect from the true efficacy. So, I think they do
21 | have to be blinded, if at all possible, but then they can
22 | go on into the long-term and just be doing a good job of
23 | getting the toxicities in the long-term.

24 | DR. STIEFEL: I agree with everything you said,
25 | but let me also talk about placebo effect in kids with

1 special needs. I want to introduce a concept of placebo
2 effect that's additive. I can tell a teacher or education
3 system that I'm going to put a child on medication -- it
4 doesn't matter what it is -- and buy that child another
5 year of placement just because of the hope and faith that
6 that medication will make a difference in terms of the
7 problems that the child is having, whether that's drooling
8 or whatever that is. You then add to that in the kids that
9 have the cognitive abilities to be able to look into that,
10 that child is also hopeful, plus the caregivers that are
11 hopeful. And I'd say 1 plus 1 plus 1 probably equals about
12 5 there. So, we have efficacy that approaches 40 or 50
13 percent in many of these medications and placebo that
14 approaches almost the same amount. So, it's very, very
15 interesting and very difficult.

16 Again, we're not representing that these are
17 simple issues. Our job is to give you information to be
18 able to address these very, very complex issues and to see
19 if, in this crisis that we are involved in, whether or not
20 there is an opportunity to perhaps do some of the things
21 that we're talking about.

22 DR. NELSON: I guess I'd like to pursue that a
23 little more because what I had heard earlier was, when I
24 had asked the question about blinding, which was really
25 meant about an assessment tool issue, that the notion of

1 | being on a medication that could potentially not be
2 | efficacious wouldn't be acceptable to parents, undercutting
3 | the possibility of that kind of trial.

4 | We had started off by saying we're going to
5 | assume efficacy, which was sort of a physiologic
6 | assumption, but now, since we have to do it for a new
7 | indication, suddenly we're back into designing an efficacy
8 | trial. And now we're back into placebos even though we
9 | started off the morning by saying let's assume it's
10 | efficacious.

11 | I recognize the regulatory impediments, but do
12 | we really think we need a classic efficacy trial? What
13 | would be the purposes of a placebo arm? I guess I'm just
14 | getting a little confused about the direction on that
15 | particular point.

16 | Would it even be acceptable? I could see an
17 | active control equivalence trial even if it's defined as a
18 | superiority to try and eliminate Bob Temple's objections to
19 | those kinds of trials. So, I guess I'm a little confused.
20 | I just want to focus on that issue a little bit.

21 | DR. CHESNEY: Could I just intervene for a
22 | moment? We're theoretically just asking directed questions
23 | and now we're getting into what they really want to hear
24 | from us. So, could we ask Dr. Kelsey to give us our
25 | mission? I think you're on the schedule for that.

1 DR. KELSEY: Yes. I'm going to go back over
2 the questions. Well, I feel like we've gone over these
3 questions several times already this morning. So, I'm not
4 sure how much new ground there's going to be, but maybe
5 this can pull it all together.

6 This has been very useful for us at FDA. As I
7 said, we're new to the issues surrounding study in this
8 patient population and these comments that we've heard this
9 morning have been very beneficial.

10 I'll go back to the questions that we presented
11 initially, and I guess, if it's okay, Dr. Chesney, we'll
12 just go question by question and discuss it that way.

13 So, the first one concerns adverse events and
14 how they can best be assessed in this population. Some of
15 the issues that I noted down here have to do with frequency
16 of professional assessment. Certainly the parents are
17 important in assessing the day-to-day impact of the
18 medication on their child. However, it's also clear that
19 sometimes the parents miss things and how often are the
20 professionals going to be involved. What sort of training
21 do the parents get to assess adverse events? Specifically,
22 in clinical trials, would you advocate use of checklists,
23 training sessions for parents, that sort of thing?

24 Would small dose-ranging safety studies be
25 appropriate in the beginning to look at small groups? We

1 | talked about the fact earlier that it might be difficult to
2 | take a subset of the overall population of people with
3 | cerebral palsy, but it might be reasonable to have some
4 | small initial studies.

5 | So, those are a couple of things that I noted
6 | after this question in my notes.

7 | DR. CHESNEY: Could I ask you to go through all
8 | the questions? We may not start at the beginning. I'm
9 | thinking we might go right away to number 2. But if you
10 | could cover all of them and the issues that you want to be
11 | sure we address.

12 | DR. KELSEY: Question 2 is the formulation
13 | question that we discussed in the last few minutes. The
14 | suggestions for the patch or reditab or sustained release
15 | or other formulations are certainly interesting.

16 | The concentration of a liquid formulation.
17 | What would be appropriate in terms of being able to titrate
18 | in very small doses? The possibility of using a couple of
19 | different dosage forms, going back to the diabetic analogy,
20 | to having a sustained release or patch type formulation to
21 | act like NPH and then supplement it with a liquid
22 | formulation as needed, analogous to regular insulin.

23 | Dosing frequency. We're going to want to have
24 | some PK studies. Even though we agree that these compounds
25 | are going to work in the same way that they are in adults,

1 the PK will be different or it will likely be different.
2 So, we would certainly want to look at the PK, and from
3 that come up with optimal dosing schedules.

4 DR. CHESNEY: Sorry for interrupting, but are
5 you actually talking about blood levels for PK?

6 DR. KELSEY: Yes. Certainly determine the
7 half-life in kids and use that as a place to start your
8 dosing schedule.

9 Question 3. Since therapies need to be
10 titrated, guidance on dosing is necessary in product
11 labeling. Please discuss the labeling tools to help
12 caregivers assess the benefits and side effects of these
13 medications.

14 We talked about this quite a bit in our
15 preparation for this committee. We started off talking
16 about who were the most appropriate people to assess both
17 efficacy and adverse events in this patient population.
18 Certainly I think we all agree that the caregivers are the
19 people who are most familiar. But there's a range of
20 antimuscarinic effects, and certainly it's complicated, as
21 Dr. Stiefel was saying, by the status of these patients and
22 polypharmacy and the rest of it.

23 What can FDA do? Looking down the road when we
24 have sponsors come to us and want to develop a product for
25 this indication, what can we do to direct them to come up

1 with something in labeling -- the broader sense, not just
2 the patient package insert? What can we do to help the
3 caregivers do the best job possible in dosing these
4 patients so that they get the benefits with the minimum of
5 side effects?

6 The fourth question. This is the ethics
7 question. Are there additional processes or procedures
8 that need to be in place to ensure the safe and ethical
9 conduct of studies in this special needs population? I
10 thought that the ethical advice was probably the clearest
11 that we got. Certainly looking back to Dr. Wilfond's
12 presentation, we're on the top row of his chart, and it
13 would be reasonable, based on the potential benefit, to
14 study these drugs in this patient population.

15 It would be desirable to have patient assent in
16 at least some patients, but it's recognized that it's not
17 possible to do that in many of them. I guess what I heard
18 was that this should be balanced. We shouldn't focus on
19 institutionalized patients alone, but that it would be
20 reasonable to do these studies in a range of these
21 patients.

22 DR. CHESNEY: Thank you.

23 I'm tempted to begin with number 2 because
24 we've already, as you indicated, done a fair bit of
25 discussing of that. That seems very kind of hard core

1 science. So, questions or further comments addressing
2 characteristics important in developing a pediatric
3 formulation. I think we're being asked also about how to
4 individualize a dosing regimen and the issue of having to
5 obtain blood samples to do PK determinations.

6 Comments? Dr. Nelson.

7 DR. NELSON: I'm trying to think through in my
8 own mind if there are other examples where you want a
9 formulation that allows you to titrate to the extent to
10 which it seems you want to titrate, but yet have a
11 sustained effect, without getting into a situation where
12 you have to create 14 different types of patches. With
13 pain and theophylline, there you have sustained release,
14 which is possible, and you're measuring blood levels. For
15 pain I tend to use morphine and other kinds of things.

16 I don't know. There are examples but it just
17 seems to be a little bit more complex. The ability to
18 titrate on a short-term effect seems to be working against
19 the desire to have a preparation that you only need to use
20 once or twice a day.

21 DR. SPIELBERG: Skip, I think the reason is
22 that we're using drugs for which the desired outcome is
23 simply a side effect, and the drugs were developed for
24 totally different purposes. Therefore, we don't have a
25 therapeutic index to deal with here. If we had increased

1 specificity for the target of interest, then you're talking
2 about a drug designed for the specific indication. Here
3 we're talking about drugs designed for totally different
4 purposes, the side effect of which is dry mouth. So, now
5 we're saying we want dry mouth for drugs that are designed
6 for other purposes, and I think that's why there's so much
7 of the struggle in terms of titratability.

8 There are novel delivery systems that can begin
9 to get into these kinds of things without going into any of
10 the technical details. This is why I asked the question.
11 If we wanted to solve the problem, forgetting what's out
12 there now, do we want new drugs or do we want to try to
13 struggle with the old drugs? If we are struggling with the
14 old drugs, indeed, what you're doing is looking for one of
15 a myriad of effects of the drugs and trying to get to a
16 tolerable point where you get that side effect, if you
17 will, predominating over the other effects of the compound.
18 It's going to be very hard to do, and therefore you're
19 going to need a great deal of individualization with
20 respect to dosing.

21 DR. CHESNEY: That's probably an important
22 question to answer because the agency has been asked about
23 this drug or about this group of drugs. So, from their
24 point of view, they need to look at this drug and the
25 current formulations.

1 DR. SPIELBERG: In which case, it's going to be
2 very, very hard and require a great deal of
3 individualization of therapy. As Skip put it, it's
4 basically a series of tolerable or intolerable side effects
5 in an individual patient, each of which needs to be in the
6 context of all the other medicines that the child is taking
7 since a huge number of the compounds that they are likely
8 to be taking will also have autonomic effects.

9 DR. CHESNEY: One problem, though, is that this
10 is not a large market, and how do you invite a manufacturer
11 to develop a new product? And won't that take just as long
12 as it might to work out all the details with this product?

13 Dr. Wilfond has something burning to tell us.

14 DR. WILFOND: I was just thinking of your
15 comments. It certainly strikes me that it's not at all
16 uncommon to have to make very challenge individual
17 decisions about drug level. Theophylline is a perfect
18 example of that.

19 But with regards to your comment about
20 exploiting a side effect and that being problematic, that's
21 a fairly standard thing. I'm thinking Viagra, minoxidil.
22 There are lots of examples where drugs developed for one
23 purpose are used for one of their side effects. I don't
24 think it's inherently a problematic thing.

25 DR. SPIELBERG: But it's entirely dependent on

1 therapeutic index, and it's dependent on the dose and the
2 serum concentrations associated with the desirable and
3 undesirable side effects and the ability to separate those
4 out for an individual compound. That's the quandary.

5 DR. CHESNEY: Dr. Mathis.

6 DR. MATHIS: Just in response to your question,
7 Dr. Spielberg, obviously we would welcome any new approach
8 to treating this problem. But it's important to remember
9 that the antimuscarinics have been used successfully for
10 this indication off label, and so I think that we'd also
11 like to encourage sponsors to develop those products which
12 are currently being used, as well as welcoming novel
13 approaches. But there aren't any pediatric formulations of
14 the antimuscarinics, and any development in that area would
15 be very helpful.

16 DR. CHESNEY: Dr. Fink and then Dr. Gorman.

17 DR. FINK: As I listen to the discussion as it
18 occurs, it also seems clear that the other thing we need to
19 do is encourage the academic community that we really need
20 to know more about this clinical problem because although
21 we're focusing on drooling and the salivary gland, I would
22 at least maintain that this is really more an issue of
23 upper airway function in the neurologically impaired
24 individual. If you look at some of the simple things that
25 could explain day-to-day variation in drooling, nasal

1 congestion. If your nose is stuffy, it hurts to swallow,
2 and I'm absolutely sure in neurologically impaired
3 individuals, upper airway obstruction, particularly of the
4 nose, has a big impact on their drooling. So viral
5 infections, allergies, untreated allergic rhinitis,
6 untreated perennial rhinitis is going to have a bit impact
7 on the amount of drooling. So, one of the things we need
8 to say is we need to have a better understanding of this,
9 better ways of assessing which components are leading to
10 it.

11 We haven't even touched on the sleep disorders
12 that are related to this, which is a whole other bag of
13 worms, but maybe dwarfs nasal congestion and so on
14 tremendously. Maybe we shouldn't even be looking at
15 drooling. We should be looking at the sleep effects of
16 this whole constellation of symptoms because if you improve
17 sleep and patients are more alert during the day, maybe
18 they'll swallow better.

19 DR. CHESNEY: Dr. Gorman.

20 DR. GORMAN: First a comment to the experts and
21 individuals who advocate for the children and patients with
22 the condition of drooling. I heard several times this
23 morning for a change in the paradigm or people to push the
24 envelope. I'm now sitting on an FDA panel where I have the
25 agency asking me to consider developing clinical trials for

1 an off-label use in a group of people this drug has not
2 been approved for. So, I think this is a very proactive,
3 different group of people. The paradigm has, in fact,
4 changed and I think that needs to be recognized. If I have
5 now stepped over some legal boundary and a thunderbolt is
6 about to hit me, I'm sorry. But this is very different
7 from the usual behavior that we think of in our regulatory
8 bodies. This is not what they usually do.

9 Secondly, the word "titration" has been used
10 interchangeably between the desired outcome, which is the
11 control of drooling, and the fact that this has a very
12 steep dose-response curve and a very narrow therapeutic
13 index, all of which make the drugs that we're looking at
14 incredibly difficult to titrate for the desired effect
15 without the adverse event. I think if we had a drug with a
16 higher therapeutic index and you could control drooling
17 without constipation or tachycardia, that we wouldn't be
18 having this discussion because parents or caregivers,
19 whoever they would be, would reach their efficacious
20 outcome and then not have to deal with the side effects.
21 Then it would just be a matter of putting out a formulation
22 that allows parents to titrate.

23 So, I think that Dr. Spielberg's concern about
24 either whipping old dogs and trying to make them do new
25 tricks or creating a new dog becomes a very important issue

1 and goes back to whether if this is FDAMA-able. If
2 glycopyrrolate has FDAMA stuff, we can whip the dog a
3 little bit, but then you're going to have to find inside
4 our regulatory body the ability under -- this will reveal
5 my ignorance. What was this drug approved for?

6 DR. KELSEY: It was originally approved back in
7 1960 for GRD, and it's also used by anesthesiologists
8 intraoperatively to decrease secretions.

9 DR. GORMAN: As an approved use.

10 DR. KELSEY: Those are approved uses, but they
11 were only studied in adults.

12 DR. GORMAN: I guess there could be some
13 pressure put on the sponsoring company to create a
14 pediatric formulation for the drug. Some.

15 Thank you.

16 DR. CHESNEY: I'm thinking that maybe we have
17 discussed number 2. I think the committee is totally in
18 agreement with a new formulation for children, and we've
19 got some original ideas of new ones that might be
20 developed, but certainly to make a preparation that's
21 palatable, that tastes good, that feels good, and the dose
22 is appropriate to titrate small amounts.

23 So, I think unless you want more information on
24 that question, I'm thinking that the core issue is how to
25 evaluate for adverse events and then number 3, which is

1 very closely related, which is what tools to use. Is that
2 all right with you if we go ahead?

3 DR. KELSEY: Yes, absolutely.

4 DR. CHESNEY: So, what are people's thoughts
5 about how to assess the adverse events in this population?
6 I guess that goes to everything from whether they need to
7 have cardiac monitors on and, if so, for how long and how
8 to evaluate saliva production and written tools and who is
9 going to do the assessment? So, who would like to start?
10 Dr. Fink.

11 DR. FINK: I'm not sure I'm going to help the
12 discussion any with this comment, but I think that
13 potentially the most important adverse event often in this
14 group is pain or discomfort. Unfortunately, that
15 particular side effect is really only assessable either by
16 the individual, if they're able to communicate, or by the
17 caretaker. I'm a little worried that the tendency is to
18 say use outside observers. In many of these children at
19 least, outside observers tend to markedly underestimate
20 problems and symptoms, and you really have to go with the
21 caregiver. So, I guess my vote there would be we've really
22 got to have the caregivers heavily involved because
23 transient observers usually don't understand the problem.

24 DR. CHESNEY: Yes.

25 DR. FUCHS: I guess actually I want to tie

1 | questions 1 and 3 together because we're talking about such
2 | a heterogeneous population. We've mentioned subgroups, and
3 | it may be that this is a staged study because you've got
4 | children who are in home and school so that maybe you can
5 | have the patient, the parent, and school teachers do all of
6 | this assessment, and obviously the physician. Then you've
7 | got those who are only at home, so you'd leave the teachers
8 | out of this, and maybe you'll have a speech pathologist or
9 | a home care nurse who comes in and can do this. Then
10 | you've got the residential care patients who really,
11 | depending upon where they are, may not even have a parent
12 | to watch them. That is mainly a nurse or a nurse's aide.
13 | So, you've got all of these steps and these subgroups that
14 | I think you are going to have to almost study them a little
15 | bit individually and figure out all these adverse events
16 | because what may be an adverse event in one group may not
17 | occur in the other. The ones in residential care may have
18 | tons of adverse events, but no one is really able to assess
19 | them appropriately because they don't have the
20 | communication skills, they don't have a parent. So, I
21 | think we're looking at a lot of different groups and you're
22 | going to have to do this very separately.

23 | DR. CHESNEY: I think that's a good point.

24 | Now that we have PPRUs, let me ask Dr.
25 | Kauffman, could heart rate, sweating, pupillary dilatation,

1 that kind of thing "be done in a PPRU? And how would you
2 envision practically doing something like this?

3 DR. KAUFFMAN: I think those are primarily
4 objective physiologic measurements or observations that can
5 be done. I think those could be done in multiple
6 environments. I don't think that most of those
7 observations would have to be done necessarily in a
8 professional care setting. We do GI Ph probe monitoring at
9 home. We do other kinds of monitoring in the informed or
10 supervised home setting. So, I think some of this could be
11 done. Particularly if you're involved in a long-term study
12 that's been advocated here, I think we're going to have to
13 look for ways to do this in the child's life setting, and I
14 think that's doable for most of them.

15 Something that's going to be essential here is
16 for us to have a consistent, formal way that the caretakers
17 are trained to look for the most important side effects.
18 The point has been made this morning that people don't
19 tumble to the fact that something is going on as early as
20 they might have. That includes, as a part of a study
21 protocol, training the key persons to be on the proactive
22 lookout for these things, so they're trained to look for
23 constipation if that's the most common side effect.
24 They're trained to look at the pupils of the eye at
25 periodic times, maybe a certain time after each dose. I

1 think we could even train them to do a very simple visual
2 accommodation test that would be easily done by the
3 caretaker. Certainly blood pressures, pulse rates, other
4 physiologic responses that we might want to monitor.

5 I'd have to think through it, but I'm not sure
6 we would want to buy into doing extensive
7 electrophysiologic monitoring in these kids in their daily
8 life. I think it would be very disruptive and invasive and
9 probably destructive in some ways.

10 And then the kids that are able to self-report,
11 I think we could use self-report scales. There are non-
12 self-report scales, as has been pointed out earlier, that
13 are used in neonatology and intensive care units and those
14 kind of settings that do attempt to assess comfort and
15 discomfort and pain. Those could probably be adapted for
16 this kind of work.

17 So, yes, I think this can be done. I don't
18 think it has to be done in a formal study setting like a
19 PPRU, but I think that most of the PPRU sites, as well as
20 other centers around the country, have the people that are
21 expert in doing this kind of thing.

22 DR. CHESNEY: The PK studies --

23 DR. KAUFFMAN: Yes. I think the study design
24 that has the most appeal to me, listening to this
25 conversation this morning, would be the for the primary

1 efficacy. The drooling is a rapid response. You titrate
2 that. You can see the response to that fairly fast. If
3 the primary outcome variable was quantitating the drooling,
4 that could be done in a fairly short run in, short efficacy
5 period that could be blinded and comparative in parallel
6 randomized groups, and then, as was pointed out, roll into
7 an open-label longer-term study for tolerability and
8 safety.

9 The PK work could be done in that short-term
10 blinded period. And it's easy. I say it's easy. At least
11 at our site, it's easy to schedule a kid -- and it is in
12 other sites too -- to bring the child in scheduled for 24
13 hours or whatever to do it. It's technically easy. It may
14 not be easy emotionally, and there are the ethical
15 considerations. But we do this routinely in children in a
16 very child friendly, compassionate, noninvasive way so that
17 we can sample small blood samples over a 24-hour period
18 with one stick and the child is not inconvenienced or
19 uncomfortable while that's going on. So, I think those
20 kind of things are surmountable. They're challenges, but I
21 think they're surmountable.

22 While I have the platform, one thing I wanted
23 to point out is I think we have to be thinking in terms of
24 the pharmacokinetics. It's been pointed out that there's a
25 wide range of response in these kids. That could be due to

1 a number of factors, one of which is with these kind of
2 compounds that tend to be quite polar is the absorption
3 characteristics. I suspect that the absorption is all over
4 the place, even in the individual child dose to dose. With
5 this kind of molecule, typically the absorption is very
6 erratic. It's incomplete from the GI tract, and it's very
7 dependent on what else is in the gut and the formulation
8 that it's administered with. These are being given in all
9 sorts of things, ice cream and apple sauce and who knows
10 what else.

11 (Laughter.)

12 DR. KAUFFMAN: So, I think one of the things we
13 would want to consider is designing the PK piece of it so
14 that we could get a very good handle on what the absorption
15 characteristics are with the various delivery systems that
16 we decide to evolve. That may be much more important than
17 the elimination kinetics by disposition of the compound in
18 terms of explaining individual patient response. There may
19 be individual pharmacodynamic responses too that are much
20 more difficult to get at. For oral administration of these
21 kind of compounds, if I was going to put my money on the
22 thing that we're going to find most important in terms of
23 variation in response, I would be looking at absorption
24 characteristics and kinetics as the first thing to look at.

25 DR. SPIELBERG: Just to add on one more thing,

1 | because of the GI side effects, if you change small bowel
2 | motility time and gastric emptying, your absorption
3 | characteristics are going to change. So, to the extent
4 | that one child or another has more or less in the way of GI
5 | effects -- and many of these children already have GRD and
6 | GI upset from their primary disease -- that can be a major
7 | issue.

8 | DR. KAUFFMAN: This is a major argument for
9 | transmucosal or transcutaneous delivery systems which could
10 | be very advantageous.

11 | DR. CHESNEY: The other issue is the
12 | polypharmacy. Presumably the other four or six or eight
13 | drugs that they're on, leaving out the complementary
14 | medicine, are going to affect GI motility and affect
15 | absorption and so on, and every child is going to be
16 | different in that regard.

17 | A quick question, also very naive. If
18 | absorption is a factor, how many children would you have to
19 | look at? How many times would one need to look at the same
20 | child on different occasions? Obviously a very naive
21 | question.

22 | DR. KAUFFMAN: I don't think I can answer that
23 | because I don't know what the range of variability or the
24 | variance is. We'd have to do some pilot work I think to
25 | see. It's been pointed out it's a very heterogeneous group

1 and the characteristics of their gut behavior, as well as
2 other characteristics of the kids, is going to be so
3 variable that I think it's going to take more than we
4 typically would enroll in a typical PK study with otherwise
5 healthy children. So, I think we're going to see enormous
6 variability, with subgroup characteristics, and we're
7 probably going to have to be willing to look at a larger
8 group of kids than we would in many similar cases.

9 Dr. Nelson's got a comment.

10 DR. CHESNEY: I'm going to turn to the right-
11 hand side in a moment. Go ahead.

12 DR. NELSON: Ralph, if you're correct in the
13 hypothesis that absorption is a major factor in the
14 variability, you presumably then would find a dose response
15 that might be a little bit more predictable except for all
16 of the variables that have been mentioned that impact then
17 on the response of the child to the medication which would
18 involve all of the other medications, for example, that
19 would also have these same kinds of physiologic effects.
20 So, you'd have to, in working that out, end up with a
21 fairly complex study.

22 As I think about the labeling issues, I go back
23 to the slides that I think Dr. Mathis had about effects of
24 atropine in relationship to dose and the like. I think of
25 other medications that we use through a range of effects.

1 One possible outcome could be an understanding of the
2 sequence in which these side effects take place, so that I
3 would know that if I gave X dose, I get a certain response.
4 As I increase the dose, I begin to see other responses.
5 I'm thinking of dopamine. We all dial it up and down to
6 get different responses.

7 The question would be, even if it's a variable
8 dose at which you see the balance between the good side
9 effect, no drooling, and the bad side effect, constipation,
10 could you find an invariable sequence, for example, so that
11 I as a clinician would know that as I titrate up the dose,
12 certain side effects appear or disappear, depending upon
13 that level?

14 What strikes me as very different about this
15 compound compared to early development compounds is we know
16 the safety profile pretty much. We can target measurements
17 to the side effects we want to study, which is often very
18 different where we target an efficacy outcome and then we
19 say, oh, by the way, let's just see what happens in terms
20 of the safety and then we get all the adverse event
21 reports. Here you could actually target specific adverse
22 events for measurement, which is a very different setting.

23 DR. KAUFFMAN: Muscarinic pharmacology is the
24 oldest, most classical pharmacology. It's the first
25 chapter in Goodman and Gilman, and it's classic receptor

1 agonist/antagonist pharmacology with receptor subgroup
2 types.

3 So, theoretically you could do what you're
4 saying. I don't know if it would work clinically, but the
5 curve that was shown this morning with atropine is a
6 classic sigmoid dose-response curve. Theoretically we
7 would be able to do effective dose 50's for the major
8 predictable dose-related side effects and the desired
9 effect and see where in the concentration range those are
10 differentiated. Then it would at least give us a guide as
11 to what concentration effect we can anticipate. I don't
12 know in the clinical setting if that's achievable or not,
13 but it should be our goal if we can move in that direction.

14 DR. CHESNEY: I think that would be one of the
15 major contributions.

16 I was concerned. Dr. Mathis, I think,
17 mentioned this morning that you can have some individuals
18 who have no effect on salivation but have toxic effects and
19 other responses. So, it may be highly variable, but that's
20 the kind of information you could get for us.

21 DR. SPIELBERG: Remember, this particular drug
22 was developed as a GI drug.

23 A little bit of history. Otto Loewi won the
24 Nobel Prize, I think it was 1921, for cholinergic
25 transmission. The apocryphal story was he got the idea in

1 | the middle of the night, wrote it down on a piece of toilet
2 | paper and flushed it, and it took two years for the thought
3 | to come back.

4 | (Laughter.)

5 | DR. CHESNEY: That is scary.

6 | DR. SPIELBERG: I don't know if that's true.

7 | DR. KAUFFMAN: That's an argument for
8 | constipation, isn't it?

9 | (Laughter.)

10 | DR. CHESNEY: One last comment, Dr. Stiefel,
11 | and then we'll break for lunch.

12 | DR. STIEFEL: I just want to punctuate the
13 | comments that just happened. Robert Ward, head of our
14 | group, has looked at this. We've had the same discussion
15 | in preparation for this. We agree that the absorption,
16 | once removed in terms of that variable, with these
17 | quaternary amines which are the primary subjects that we're
18 | looking at, which are very polar, as you've talked about --
19 | and again, those that have much less tendency to cross the
20 | blood-brain barrier are first looking at -- I'm intrigued
21 | by Dr. Spielberg's thoughts about new directions to go, but
22 | that's probably beyond the scope of what we're talking
23 | about.

24 | We believe that if the absorption, first of
25 | all, was ever studied in these kids -- if you look at all

1 | the other things that have been done in terms of all the
2 | other medications, nobody has ever even looked at the
3 | questions that were raised. You would be horrified just
4 | from an empiric standpoint as to what you would see that we
5 | would be able to actually translate to many other
6 | medications that have absorption problems, first of all.

7 | And then, secondly, if that variable was
8 | removed -- and again, that's where my challenge to a novel
9 | delivery, either transmucosal or transdermal. If you
10 | remove that, we think that actually you would be able to
11 | develop dose-response curves.

12 | Then the only other piece is I actually do
13 | think one needs to find a balance. I think there's been
14 | somewhat of a misperception, at least from my perspective,
15 | that we want to titrate these things every minute. I think
16 | the insulin analogy is an appropriate one, but our
17 | experience has been the opposite of that. We want to find
18 | that balance over time where the drug levels remain the
19 | most consistent, particularly those with central nervous
20 | system effects, within the nervous system over time. We
21 | want to find that balance. We don't want to go up and down
22 | every day. Most families, even though they have the
23 | capacity, over time end up not doing that because they get
24 | into a vicious cycle of side effects and other sorts of
25 | things, particularly the CNS side effects. So, we actually

1 | move towards a balance and, again, think that the comments
2 | would be very, very appropriate. Just a differing
3 | viewpoint.

4 | DR. CHESNEY: Thank you.

5 | Jayne Peterson has just pointed out to me that
6 | we've completed question 2 and we're well into 1 and 3,
7 | which only leaves 4. So, if there is anybody who would not
8 | like to continue the discussion, since we do have food over
9 | here, please put up your hand. Otherwise, we'll just keep
10 | right on going.

11 | (No response.)

12 | DR. CHESNEY: All right. We'll keep right on
13 | going.

14 | Other comments, questions? Dr. Walters.

15 | DR. WALTERS: Are we going to 4 now or not?

16 | DR. CHESNEY: I think still 1 and 3, unless Dr.
17 | Kelsey tells us he has enough information.

18 | DR. KELSEY: No. I think we should finish up 1
19 | and 3 unless there is no more to be said. I said earlier I
20 | think 4 is going to be pretty quick.

21 | DR. CHESNEY: Coming to number 3, which are the
22 | labeling tools, and also to see if the committee is agreed
23 | that the caregiver should be the primary person recording
24 | the long-term information, whereas the PK data obviously
25 | and that testing would be done probably in a PPRU.

1 Any disagreement about caregivers? Dr.
2 Szeffler.

3 DR. SZEFLER: I think the importance of the
4 caregiver is to establish the baseline because it sounds
5 like the baseline can be variable. So, having a sufficient
6 period of time and a careful observer would be very
7 important to establish that baseline and get some handle on
8 the degree of variability so that you could detect an
9 effect. That's where it gets into important questions like
10 defining your response variables.

11 I have a suspicion that in these patient
12 populations and where your group could be helpful is to
13 draw upon your experience to say who are responders and who
14 are nonresponders because I have a feeling where you get
15 into trouble is when you push the dose in the nonresponders
16 and you don't have either the classification variables in
17 terms of the patient or the level of knowing when to stop.
18 That's probably where the problems come in, besides the
19 rapid absorption that can occur with things like the
20 liquid.

21 So, I think in terms of the observer, the
22 caretaker, whoever it is, whether it's the parent or the
23 foster parent, I think the care in institution is probably
24 too inconsistent and you would just have daytime measures,
25 which would miss potentially nighttime measures. So, I

1 don't know how that gets done unless there's specialty care
2 centers that do research, and there may be certain centers.
3 I don't know all the ethics of that in terms of how that's
4 checked, having outside reviews do it, but I think some
5 consistency of the observer, both in terms of the baseline
6 to get a good baseline and then the follow-up, becomes very
7 important.

8 DR. CHESNEY: Dr. Stiefel.

9 DR. STIEFEL: I don't think this is as hard as
10 we're making it. The first phase studies, which we've
11 talked about, are critical and very doable, and I think
12 they're there. They're very important not only in terms of
13 this but in terms of paving the way as to where we move
14 with many of these medications.

15 The most difficult thing that we run into is
16 actually defining the outcome that we're going to actually
17 be looking at in terms of efficacy. I think what you've
18 heard presented this morning is a broad range of outcomes.
19 For one child it will be the social victimization that
20 occurs because of the drooling, and you'll titrate that
21 very differently than a child who has main problems with
22 aspiration, titrate that very differently than another
23 child.

24 We approach caregivers just as I approach
25 training a resident. I believe that they're

1 | extraordinarily sophisticated. Many times the parents are
2 | remarkable, and we spend a lot of time training the
3 | caregivers.

4 | I think we have plenty of outcome tools
5 | actually from a broad range of things to be able to assess
6 | these things, and you've heard a broad range of
7 | presentations. If you put that together in terms of a
8 | cumulative whole, we have the tools to be able to assess
9 | the longer-term second phase studies.

10 | So, the real issue is actually defining what is
11 | the outcome that you're going for in terms of efficacy when
12 | you move and define efficacy beyond just is there an
13 | antimuscarinic response. Once that's defined, I actually
14 | think it becomes very easy, and we find that the difficulty
15 | is determining what outcome we're going for and then
16 | tracking that.

17 | So, once that's done, my only plea is, even
18 | though we talk about the importance of the caregiver, I
19 | think the importance of a consortium and people who are
20 | actually trained in these areas to be able to help the
21 | family and the child determine what those outcomes are and
22 | then have the sophistication to be able to partner not in
23 | an objective means separate from, but to be able to partner
24 | in a relationship and team to be able to look at those
25 | things. I think it's very doable and I think we can move

1 forward in that sense. So, I don't know if that helps.

2 DR. CHESNEY: I think you and Dr. Kauffman have
3 said the same thing, which is to train the caregivers in
4 all the tools they need.

5 Discuss the labeling tools to help caregivers
6 assess the benefits and side effects. How much detail do
7 you want from the committee on that particular issue?

8 DR. KELSEY: Well, I guess we're, first of all,
9 looking for agreement that this is a good approach to take,
10 that the caregivers are going to be the ones that are
11 titrating the dose for these patients, and that it's
12 valuable to provide them with material to train them. We'd
13 also be interested in anybody's experience with this sort
14 of thing for other products. We don't have it in our
15 division. But we think that this is a good idea and we
16 assume that you will agree with us on this.

17 DR. CHESNEY: I think everybody is in agreement
18 that this is a good way to go. Experience. Dr. Fink and
19 then Dr. Szeffler.

20 DR. FINK: We may be saying the same thing.
21 With asthma drugs, there's a very positive trend, which is
22 there's a parent insert with the medication, with the
23 inhaler, the discus, or whatever it is that is written at a
24 5th or 6th grade level and is totally separate from the
25 package insert. It has no overlap and is educational to

1 the parent but is not the FDA-required package insert. I
2 think you would want something similar that was very parent
3 oriented, 5th, 6th grade level, very straightforward, and
4 not more than maybe a page or two pages in length because
5 no one will read it if it gets too long.

6 DR. KELSEY: This isn't part of the package
7 insert, but is this an FDA-approved part of the label?

8 DR. FINK: I don't honestly know the status
9 with the asthma drugs. I think they are parent inserts
10 saying here's how to use the device. They are not
11 technically part of the package insert, and I don't know if
12 they are FDA reviewed or not.

13 VOICE: They are.

14 DR. KELSEY: They are. Thank you.

15 When we talk about labeling, it really extends
16 beyond just the package insert, the container itself and
17 any other things that we've reviewed or included in that.

18 DR. CHESNEY: Dr. Szefler was next.

19 DR. SZEFLER: I was going to say, you were
20 asking about partners. I think the potentially obvious
21 partner would be whatever division handles psychoactive
22 medications because you'd want to get some handle on
23 behavioral testing. Motion testing devices. I think you
24 had some questions about adverse effects in terms of
25 activity. There are motion detectors, video assessment

1 type things. So, I think they have the tools because they
2 deal with it in terms of behavior disorders in children.
3 So, you might adapt some of those tools to this type of
4 testing.

5 DR. CHESNEY: Dr. Danford.

6 DR. DANFORD: I agree with Dr. Fink's remarks,
7 at least in concept, that having a short 5th to 6th grade
8 level tool to help educate caregivers would be ideal. I
9 think that that might not be practical or realistic in the
10 current problem because I can foresee an insert that's
11 about yea thick with discussions of all of the possible
12 interactions with the various drugs that these individuals
13 are already taking, interactions with other organ systems
14 that are already diseased and troublesome, and finding that
15 it would very quickly become very complicated. The problem
16 is trying to decide where on the spectrum between no
17 guidance and the textbook of developmental disabilities and
18 their pharmacology that we want to settle on the
19 educational insert for caregivers.

20 DR. CHESNEY: I think probably a lot of that
21 information would come from the studies themselves and how
22 the caregivers could be best taught and how they learn best
23 and so on. Maybe that would come out of the process of
24 studying the drug.

25 Other comments or questions about labeling?

1 (No response.)

2 DR. CHESNEY: I think we can go on to question
3 4. Dr. Kelsey?

4 DR. KELSEY: Yes. This has been very helpful,
5 but I agree I think we can move on to the ethical one,
6 number 4.

7 DR. CHESNEY: So, number 4 is in front of you.
8 Are there additional processes or procedures that need to
9 be in place to ensure the safe and ethical conduct of
10 studies in this special needs population?

11 Dr. Wilfond, do you want to make any further
12 comments to what you've already made?

13 DR. WILFOND: I'll make one comment, one
14 addition to my previous comments. I mentioned that the
15 studies that I was envisioning were going to be ones that
16 were offering the individual subjects prospective direct
17 benefit with regards to the regulations. But actually, of
18 course, the PK studies, if they were done separate from a
19 longer-term study, would not count as that, and the
20 interventions for the PK study would also be separate from
21 that. Nevertheless, I don't think those would actually
22 pose any barriers to doing PK studies because I think the
23 risks of those are within the guides of the regulations.

24 DR. CHESNEY: I think Dr. Walters and then Dr.
25 Goldstein.

1 DR. WALTERS: This is actually a very
2 interesting test case for the revised Declaration of
3 Helsinki that came out of the meeting in Edinburgh last
4 October. Would we say that a proven prophylactic,
5 diagnostic or therapeutic method exists for the treatment
6 of drooling? If it does, then according to that guideline
7 coming from one medical association, one should not, from
8 this point on, conduct placebo-controlled studies.

9 DR. GOLDSTEIN: I would offer the opinion that
10 one does not exist that meets the necessary criteria, and
11 therefore, even though I have serious reservations about
12 the use of placebo, it could I think fall within this.

13 But in terms of question 4, somewhere in the
14 material that was sent to me, the question of institutional
15 review boards and their competency was raised. The members
16 of most institutional review boards have extraordinarily
17 little experience with dealing with these special
18 populations. I would believe that one would need to look
19 very carefully at what requirements would be needed at the
20 institutional review board level to make certain, one, to
21 protect against using other criteria or criteria used in
22 other examples that really don't fit this special
23 population. And that's both a pro and a con. That
24 institutional review board could require certain standards
25 that are really not applicable to this population or might

1 not require enough standards that would be necessary for
2 this population. So, I do respond to the question, will
3 there be a need -- I don't want to suggest that it be
4 parents or not parents, but there will need to be specific
5 expertise on institutional review boards when addressing
6 this particular group of studies.

7 DR. CHESNEY: That is issue B on the list of
8 questions. Does the FDA have jurisdiction over who should
9 review these studies? Can you tell the company that the
10 review has to include people with expertise in this area?

11 DR. KELSEY: We can certainly influence
12 companies. To tell you the truth, I'm not sure whether we
13 can absolutely require it, but we can certainly encourage
14 sponsors to go to an IRB that has the appropriate
15 expertise.

16 DR. CHESNEY: Dr. Nelson.

17 DR. NELSON: I always love to comment on IRB
18 issues.

19 Current regulations actually require IRBs to
20 have sufficient expertise to review protocols. If an IRB
21 feels it lacks that expertise, they're under a regulatory
22 requirement to get it. Now, the problem is do they think
23 they lack the expertise.

24 I think this is a broader issue than simply
25 this population. I would argue that there are IRBs

1 approving protocols for the inclusion of children that lack
2 a pediatrician. So, I think if the FDA wants to step into
3 this, it should. Does it have regulatory authority? it
4 does under ICH E-11. It does under the Good Clinical
5 Practice Guidelines which also specifies that the IRBs are
6 supposed to have expertise. Whether one wants to be more
7 directive about the nature of that expertise would be the
8 question. The regulatory authority is there.

9 I would agree with the comments. So, it's not
10 a question of understanding. It's a question of
11 appreciation of, in fact, whether that individual IRB lacks
12 that expertise.

13 DR. CHESNEY: Thank you.

14 Would anybody on the committee disagree that
15 the FDA should strongly suggest to sponsors that they be
16 sure the IRB has individuals with this kind of expertise on
17 them? Would anybody disagree with that?

18 DR. WILFOND: I'm not disagreeing but I have
19 another related point that may be a stretch. So, I'm just
20 going to throw this out.

21 One could consider, for a study like this,
22 having a DSMB. Let me explain why I say that. Not because
23 I think the adverse effects are likely to be so serious
24 that the trial would be stopped during the course of it,
25 but one of the things that DSMBs can do, particularly in

1 | the design of a trial, is be a central group to ensure that
2 | the safety of a trial is designed in such a way, and that
3 | group could have a wide range of expertise outside of the
4 | study developers. So, when it got to the IRB, even if you
5 | had an IRB that was falling asleep at the wheel, it's not
6 | likely they would be approving something that was really
7 | going to cause problems.

8 | DR. CHESNEY: Any comments about DSMBs? Dr.
9 | Nelson.

10 | DR. NELSON: I think there a good thing. Now,
11 | whether you need it in this case, one could -- I guess it
12 | would be worth trying to isolate what is it that concerns
13 | us about the fact that an IRB may or may not have
14 | expertise. Will they approve it for a subset of the
15 | population that's inappropriate? For example, a local
16 | group home. I mean, really beginning to focus on what is
17 | at risk here or not. I guess I'm not as clear about that.

18 | Or will it be that protocols will begin coming
19 | out that aren't really well designed, in which case you get
20 | in more towards a collaborative group effort. The
21 | oncologists have a fairly good system for designing good
22 | protocols, and I'm not that worried that an IRB might
23 | approve a COG protocol inappropriately. I'm more worried
24 | that someone might perform it who can't do it in an
25 | investigator sense. So, I think we might want to think

1 through what it is we're trying to prevent or not prevent
2 to happen at the local level, and whether you need a data
3 monitoring committee to fix that would be the question.

4 DR. CHESNEY: Dr. Szeffler.

5 DR. SZEFLER: I think the DSMB is an intriguing
6 suggestion because I think they serve three purposes. One,
7 they review the protocol again. They look at the body of
8 the people conducting it. Then they also have the
9 privilege of looking at the data as it's evolving. So, if
10 there are any concerns about a product in terms of its
11 safety or performance, they have the ability before the
12 investigators do, and they put some time lines in terms of
13 the company looking at that before you complete the study
14 and then assemble all the data. They will have time tables
15 built in where we would like to see safety and performance
16 and set up some time table of variables. So, it's kind of
17 a monitor that assures that major things or
18 disproportionate things don't go on. So, I think that's an
19 intriguing application.

20 I think I brought up before I don't know how
21 research is conducted in the special populations in terms
22 of the IRB limitations. A lot of institutions have their
23 own IRBs. Is this one that needs to go to an outside IRB?
24 Is that any kind of ethical concern? So, I don't know how
25 those situations are handled.

1 DR. FINK: I don't know if IRB is as good as it
2 should be, and I sometimes worry about that. But as I read
3 through the special needs description, it strikes me that
4 it is not at all different from the premature infant, and
5 most academic IRBs routinely consider interventional
6 protocols in premature infants that seem to have all the
7 elements of ethics involved in them in terms of cognitive
8 dysfunction and maybe even in the premature infant, the
9 question of does the parent even speak on the best behalf
10 of the child. So, I'm not sure what makes this really very
11 different from what we're routinely doing in our IRBs that
12 we need to put in special safeguards.

13 DR. NELSON: I suspect everyone around the
14 table here, though, comes from institutions that have a
15 fairly high pediatric presence and profile. I'm not
16 worried about probably the people around this table. It's
17 a question of what goes on in settings where there wouldn't
18 be that kind of pediatric expertise. Developmental
19 behavioral pediatrics is a very under-represented
20 subspecialty where you may have children with disabilities
21 who are, in fact, in a setting where they don't have much
22 access to that kind of specialty advice or consultation
23 where trials could be conducted without the kind of
24 expertise sitting around this table.

25 So, I don't think of a pediatric institution or

1 a pediatric rehab institution as being what we're talking
2 about as a best practice standard. It's would you put
3 something in place that could provide a floor that we're
4 talking about.

5 But I would agree. I don't think I would need
6 much special expertise to do this on our IRB.

7 DR. CHESNEY: I think we would all strongly
8 support that whatever IRB was involved that there was
9 demonstrated expertise in the care of these children, and
10 if it was something they felt they could address best with
11 a DSMB, then that would be an alternative approach.

12 Yes, Dr. Walters.

13 DR. WALTERS: The one area where FDA does
14 currently require DSMBs is in research involving emergency
15 interventions, and that was part of the total package of
16 rules that was passed.

17 When I was reflecting on ways in which this
18 arena might be similar to and different from, there's not
19 the press of time that there is an emergency situation. On
20 the other hand, there is a spectrum of degrees of
21 competence in the population that will be involved in these
22 studies. So, I actually think that a DSMB for an area
23 that's quite new, rather uncharted territory in pediatrics
24 might be a good additional check and safety mechanism.

25 DR. CHESNEY: It sounds like our ethical

1 expertise is coming down on the side of DSMBs.

2 4a. Can I just be sure of what I heard, which
3 is that we do not think that we should restrict this to a
4 subset of patients who can communicate verbally or by
5 keyboard? Is that correct?

6 And C, should there be independent assessors?
7 I guess we all agreed that the caretakers could be trained
8 and so on. Is there any point at which we feel like there
9 should be independent assessors involved in this process?
10 Dr. Nelson.

11 DR. NELSON: I guess I heard two separate
12 comments. One was independent; the other was blinded. And
13 we sort of went back and forth at times, but certainly not
14 exclusive. I think if you want to make sure the data
15 you're collecting, particularly where the endpoints involve
16 variable judgment, you're really not questioning the
17 judgment of the parent. Just like a qualitatively study,
18 you usually feel better if you've got two people and you
19 get interrater reliability. Those are the issues you're
20 dealing with. And that wouldn't be for all of your outcome
21 variables. It would just be for those that are more
22 judgment based.

23 DR. CHESNEY: Dr. Fink.

24 DR. FINK: I think the interrater reliability
25 is really a key issue here because one parent doesn't want

1 any drooling, a wet chin is a problem, and they're going to
2 be a child like we saw today. Another parent may say if I
3 can put one towel under the child at night and that
4 suffices for the night until 8:00 a.m., that's acceptable.
5 So, there may be very different goals of the different
6 assessors. I'm not sure how you standardize that, but that
7 would be critical because they may have actually very
8 different goals in mind as to what's acceptable outcome.

9 DR. CHESNEY: That's a good observation because
10 that goes along with what you were saying, which is -- I'm
11 blocking on what it was you said, but they were directly
12 related.

13 DR. STIEFEL: Definition of the outcome.
14 That's the major issue. And my argument is it doesn't have
15 to be the same. It has to be defined, though, and then
16 determine whether or not there is an outcome.

17 DR. CHESNEY: Right, thank you. That was it
18 precisely.

19 Dr. Wilfond.

20 DR. WILFOND: I think that it's possible even
21 if different parents have different desired outcomes, they
22 still might be able to reliably make an observation about
23 whether or not the chin was dry or whether or not they had
24 to put a towel under the neck. That's really what our
25 question is. Can we obtain reliable observations on what's

1 | occurring? Then later on we can decide what's the
2 | appropriate goal that would count as being as efficacious.

3 | DR. CHESNEY: That's a good point.

4 | Dr. Stiefel.

5 | DR. STIEFEL: Sorry. I have to be brief, but I
6 | also have to bring in the other thing that we practically
7 | are running into, which is tied into IRB, but not
8 | necessarily related to. But it comes back to the human
9 | services, human rights issues that I addressed earlier.
10 | We're actually at the point where studies get stopped and
11 | slowed down, particularly for kids that receive both
12 | federal and state funds through the state agencies of
13 | disabilities. They again have not IRB but have human
14 | rights issues that have to be addressed, and we find that
15 | if there's not synergy between the IRBs at our centers --
16 | back to your comments, we always have that tension of
17 | competency and representation and other things. But most
18 | of the major centers are looking at that. It's the other
19 | issues that are there. There's a long history of abuse,
20 | sterilization.

21 | This is really, truly a distinct special needs
22 | population that we're seeing here, and those rights cannot
23 | be and the history cannot be separated from what's going on
24 | at this point. We have found that actually we do all the
25 | other things, have similar sorts of things in regards to

1 the DSMBs and other things in place, and then get shut down
2 by not having worked with the human rights folks.

3 So, it's something you just need to be aware
4 of, not that it's your job to fix that, but to be aware of
5 that in the process. As you put up each hurdle that we
6 have to go through to be able to do studies, there is
7 extraordinary disincentive to ever go through that. And
8 that's an issue.

9 DR. CHESNEY: Could you clarify that a little
10 bit? How does one go about finding out who is responsible
11 for human rights as you were referring to them?

12 DR. STIEFEL: Well, let me make it personal.
13 I'm the medical director for our state human rights agency,
14 and I didn't think about it, in terms of our studies, that
15 I ever needed to run those by human rights even though I
16 know that that's there and I sit on the human rights
17 committee. We just assumed if we went through the
18 university IRB process that that would be sufficient. That
19 was a very incorrect, naive, and also disrespectful
20 assumption on my part.

21 So, I don't think people do know. Again, I
22 think it's something that comes out usually in retrospect.
23 People are involved in studies and then these issues are
24 raised either by a parent or by a consumer or someone else,
25 and then it has to be addressed retrospectively. So, it's

1 a huge issue, and I don't think there is any standard.

2 If you look at it state by state, these are
3 different regulations depending upon whether or not the
4 disability service is part of mental health or part of
5 other sorts of things. There is no standard across the
6 country. So, other than saying people who are involved in
7 research in these areas need to be respectful and conscious
8 of this and find out what their local climate and culture
9 is, I don't know what to say beyond that other than that
10 needs to happen. And I am the person who should have known
11 that the best and it happened.

12 DR. CHESNEY: So, it would be your state
13 disability office or?

14 DR. STIEFEL: I'm assuming that, but again
15 remember that that doesn't always exist in all states.
16 Sometimes the mental health and disability are combined.
17 So, it's not just a general thing, but there usually is
18 something at the state level in terms of accountability.
19 Remember, though, many times those things trickle down from
20 federal sort of mandates, which I don't know the specific
21 regulations. But we should probably define that as part of
22 our opinion.

23 DR. CHESNEY: Would that be important only if
24 you were considering enrolling children in a state funded
25 institution, or if you had all private patients, it would

1 still be an issue?"

2 DR. STIEFEL: Most of my private patients
3 receive respite, other sorts of resources from things that
4 are both entitlements and not entitlements that come
5 through Medicaid super waivers. Again, it's the Medicaid
6 super waiver part that then allows for these kind of things
7 to come into issue.

8 DR. CHESNEY: Has the Academy ever written a
9 statement on this type of issue, which is how do you get
10 through all the hurdles that are out there for doing
11 research on children with disabilities? It seems like that
12 might be a statement to consider for the section.

13 DR. STIEFEL: I will take that back to the
14 section. I have to be honest and say I don't know. I can
15 bring that back to the group at a later date.

16 The American Academy of Child and Adolescent
17 Psychiatry, again talking about that interface, and the
18 American Psychiatric Association have put out guidelines,
19 along with HCFA guidelines, which were updated. So, people
20 have put out guidelines for basic sort of research and
21 basic sort of need to serve this underserved population.

22 But specifically to what you're talking about,
23 I haven't read anything coherent and cohesive enough to be
24 able to do that, not that that doesn't exist. But I will
25 get that information back to the committee as appropriate.

1 DR. CHESNEY: Dr. Walters.

2 DR. WALTERS: I'm trying to think for a moment
3 outside the box of our mandate. I'm wondering whether
4 there are going to be parallel studies conducted in adults
5 while these studies in children are being done, or whether
6 there's any particular reason why it wouldn't be a good
7 idea to be conducting studies in adults at the same time
8 that the studies in children are going forward.

9 DR. STIEFEL: This is more complex because in
10 developmental disabilities we follow the education system
11 which provides services up to 22 years of age, and most
12 medical services geared around that transition to adult
13 systems are very problematic. I actually agree with you.
14 It's beyond this committee obviously, but these things also
15 need to be studied in adults, for the record.

16 DR. CHESNEY: Dr. Kauffman.

17 DR. KAUFFMAN: Just a quick answer to your
18 question about guidelines. The Academy of Pediatrics
19 guidelines on ethical guidelines for studies in children
20 from the Committee on Drugs has a section on vulnerable
21 populations. It's fairly general, but it does address the
22 essential issues that one needs to bring into play when
23 you're dealing with especially vulnerable populations. I'd
24 refer folks to that too.

25 DR. CHESNEY: Thank you.

1 Dr. Kelsey, how are we doing?

2 DR. KELSEY: I'd say great. I feel like you've
3 worked hard for us today, and we've learned a lot. I
4 appreciate the comments and the time that you've taken to
5 help us with this. As far as I'm concerned, we've gotten a
6 lot of information and the questions have been adequately
7 answered. So, unless anybody else has anything to say, I
8 feel like you've done your job.

9 DR. CHESNEY: If no one else has any comments,
10 Dr. Murphy, did you want to make any closing remarks?

11 DR. MURPHY: Thank you.

12 DR. CHESNEY: Thank you, Dr. Murphy. Really
13 nothing else?

14 DR. MURPHY: Really nothing.

15 DR. CHESNEY: Dr. Hudak had a question and then
16 I have something to tell you about. Then I think we're
17 done. Dr. Hudak.

18 DR. HUDAK: Dr. Murphy or Dr. Kelsey, Dr.
19 Mathis, it's been a very good conversation today. A lot of
20 intriguing ideas back and forth. I think I speak for a lot
21 of members of the committee. We come to these discussions,
22 we exchange a lot of information, and then at least I don't
23 get a whole lot of follow-up as to where it goes after
24 that. I understand there might be some constraints in
25 terms of what information can be shared back.

1 But could you tell us what is the next step the
2 FDA is going to take on this? Is it going to be as a
3 request to a drug company or drug companies to provide new
4 formulations, to conduct further research? Where is this
5 going to go on a practical level?

6 DR. KELSEY: Well, of course, we can't talk a
7 lot about specific interests and that sort of thing, but I
8 can tell you that I didn't just wake up in the middle of
9 the night one night and say, gee, this is an issue that I
10 think that we should go and ask an advisory committee
11 about. So, we have come to you because some questions have
12 been raised, and we're trying to get ahead of the curve, if
13 you will, and get your advice, try to define the issues so
14 that as the process moves forward, we will be well prepared
15 to help sponsors that are interested in developing these
16 products to design their trials well, and we'll be
17 comfortable that we've covered the ethical as well as the
18 design issues when we give the advice.

19 I don't have specific plans about promulgating
20 the transcript of this meeting, but that's certainly
21 something that we can think about doing to get the word out
22 to the research community that we are interested in this
23 sort of thing.

24 DR. CHESNEY: Dr. Murphy.

25 DR. MURPHY: Again, whenever we bring a general

1 | topic, we usually do try to develop some consensus
2 | statement. With the ethical issues particularly we have
3 | tried to do that.

4 | It does have impact. Maybe you all don't see
5 | it in your daily work, but we see it because we don't have
6 | people submitting PK studies done in East Europe on
7 | children who aren't going to derive direct benefit, which
8 | we were seeing, because we will not accept that data. It's
9 | not that we won't accept data. I've been told I can't say
10 | that. We will definitely accept the data, but we will not
11 | use it to grant exclusivity.

12 | So, the issue of what do we do with this. I
13 | think you bring up a very good point. We try to provide
14 | feedback in the way of the consensus statements as to what
15 | we think the committee said. Those do go up on the Web,
16 | and even if you're not assiduously scrolling through the
17 | FDA website, the companies are.

18 | You don't have a specific product coming out of
19 | this committee like you do many others. So, you sort of
20 | know what happens from a product.

21 | So, if we have a better way, if there is some
22 | sort of additional process that the committee would like to
23 | consider undertaking, we could take that issue back to the
24 | Advisors and Consultants staff in the FDA as far as is
25 | there anything else we could do because the transcripts are

1 | made available. They are public, and that is something we
2 | do, again, provide the public.

3 | DR. HUDAK: I think the one observation that I
4 | would make -- I think, again, I speak on behalf of the
5 | committee -- is that we have very general discussions, very
6 | broad issues. I think that's one thing the committee does
7 | and I think does well.

8 | I think the other opportunity for the committee
9 | or subcommittee or whatever might be -- and, again, I don't
10 | know what the legal constraints on this are. But when
11 | these things do percolate back with specific -- you send
12 | out specific requests. You get back specific proposals.
13 | In terms of reviewing those specific proposals, because I
14 | think a lot of us have expertise with the actual trial
15 | design, statistics, implementation, those sort of issues
16 | that we work with on a daily basis, if the FDA is ever in
17 | need of having that sort of input from an external
18 | committee, I think this committee would be a logical choice
19 | to bring that up before.

20 | DR. MURPHY: I think because we are dealing
21 | with the implementation of the exclusivity and rules, we
22 | don't have an approval product, and that is very specific
23 | questions about that product that we would bring. It
24 | doesn't mean we won't have for the future, but we're sort
25 | of building our infrastructure right now.

1 The other thing, just to remind you guys, is
2 you did contribute, as I pointed out, to the fact that we
3 don't ask for studies to be done for sleep disorders. So,
4 that's on the waiver list.

5 In our updates, we try to point out the impact
6 of your discussions, but I'll try to make sure we follow up
7 with you on the hepatitis C, if we issue any written
8 requests or the types of trials that we end up asking for,
9 and the same thing in this area in the future.

10 DR. CHESNEY: Dr. Gorman.

11 DR. GORMAN: Perhaps an area where we could be
12 specifically helpful in terms of specifics is to review
13 publicly available templates that the FDA has that are
14 public information on the website to see that they are
15 pediatric friendly if not pediatric specific.

16 DR. MURPHY: We could do that, but you have to
17 realize that we also have another body of experts, the
18 adult hypertensive people or the adult oncologists. Some
19 of these have already gone through some of those groups
20 too. So, we tried to get certainly the pediatric people
21 and the oncology people together. If you have templates
22 that you think we should review, we have to combine the
23 sessions with the other body of experts. That's all I'm
24 saying. So, we try to do that.

25 DR. GORMAN: I guess I wasn't so much

1 suggesting that we change the total focus of any template,
2 but more just look at the specifics that pediatric IRBs and
3 researchers might have difficulties with.

4 DR. MURPHY: Okay. If you guys have particular
5 points or concerns that you would like discussed -- that's
6 one of the reasons we are consulting you -- we'd like to
7 know what they are, and we will put together a meeting on
8 it. What we'll probably do, if we get a lot of them, is
9 we'll probably put them together and send them back to you
10 and say, you're going to have to prioritize them, or we'll
11 prioritize them and say, do you agree with our
12 prioritization? That would be great. I want to indicate
13 we think that's part of the role of this committee is to
14 help us develop these areas. So, if there are specific
15 points that you want brought forth, let us know.
16 Communicate through Jayne.

17 DR. FINK: I guess a question. Today clearly
18 we identified that there's this fairly large population.
19 There's a poorly understood issue of drooling, upper airway
20 function, sleep disorders. It would seem like some
21 communication with groups like MCH or NIH, that this is an
22 area that's been identified where additional research would
23 be highly desirable, would be a nice outcome.

24 DR. MURPHY: Yes. Actually I will just come
25 out and say the level of the discussion has been so good

1 and the participation externally so poor -- I'm very
2 disappointed in the public participation -- that we do need
3 to find a way of including. Maybe we need to do a better
4 job of letting people know about these meetings. I'm sure
5 everybody doesn't read the Federal Register. It's just
6 been a tremendous disappointment considering the
7 discussion, the number of people who heard it. I think
8 that is one thing we need to look at.

9 We have a problem because we can't notify one
10 group and not every other group. So, if we notify
11 somebody, we have to make sure we notify everybody.

12 Yes, sir.

13 DR. GOLDSTEIN: I've just come from two days of
14 meetings at NIH in which an inter-institute NIH task force
15 was reviewing the status of information leading up to the
16 potential development of trials on spasticity, rigidity,
17 and dystonia. There's a reasonable probability that this
18 NIH inter-institute task force -- and it's child health,
19 neurology particularly -- will become a working task force.

20 In following up one of the suggestions that was
21 made, I think it might be extremely valuable to that group
22 and to the FDA to begin to share some information about
23 this conversation because if that group, in fact, decided
24 with NIH funding to do a multi-institutional trial and
25 developed the protocols, et cetera, I think it would answer

1 a fair number of the problems rather than relying
2 completely upon industry to develop the background on this.
3 It's just fortuitous that within one week two separate PHS
4 agencies are addressing similar kinds of issues. And that
5 would be an operational unit. So, I would urge you to
6 consider discussing, even informally with that group, the
7 possibility of it undertaking this as an area of priority
8 research.

9 DR. CHESNEY: Dr. Nelson.

10 DR. NELSON: It's a quick question and then a
11 reinterpretation to make sure I heard you.

12 Are all the templates on the Web? I know a
13 number of them are, but is that the complete list of
14 currently developed templates?

15 DR. MURPHY: Yes. There are only a limited
16 number of templates. If we have not developed a template,
17 it is either because the diversity of the products for that
18 disease were such that we did not think we could apply a
19 template or that the level of knowledge was so different
20 amongst the classes that we felt we could not apply a
21 template, or that we just haven't had enough activity in
22 that area to develop a template. So, there are numerous
23 reasons why there may not be one.

24 DR. NELSON: Perhaps it might be part of the
25 Academy's recommendations that written requests, for

1 example, could be a public document, but at the very least,
2 templates are and that would be one arena. But basically
3 your response to Rich was go to the website and read them.
4 If you think there are some issues there, that we can then
5 communicate that back to Jayne and to Joan as a way of
6 suggesting future agenda items.

7 DR. MURPHY: Right.

8 And just one follow-up on one statement. We
9 do, again, make efforts to coordinate with other Public
10 Health agencies. As you've heard, there are really only
11 three of us -- well, two people who work at this full-time
12 on pediatrics, and it's a matter of trying to learn all the
13 other players and get everybody involved. Dr. Rodriguez
14 has just joined us in the past year as our science
15 director. So, I get to turn to him and say that he can
16 help us develop some of this liaison. He's already very
17 active and participating with the PPRUs and bringing back
18 some of the development issues that they have, dealing with
19 other agencies. So, we will continue to improve in
20 developing those liaisons.

21 But I would request the opposite too, which is
22 if people know of experts in the field in other agencies,
23 please send them to us. My e-mail address is murphyd and
24 Bill is rodriguez@cderr.fda.gov. We will then try and
25 connect up with them. We did a lot with NIMH on the

1 | development of neuropsych. We've done a lot with NCI with
2 | the development of cancer products, oncologic products for
3 | children. So, we know there's a lot more to be done, and
4 | if you have experts that we could develop relationships
5 | with, please do forward that information to us.

6 | DR. CHESNEY: Dianne, one thing that I think
7 | came out a little bit yesterday and that you heard a little
8 | bit today is that the committee would like to feel maybe a
9 | little more involved in general issues, and the template
10 | discussion is one of those. Rather than just coming to
11 | talk about hepatitis C or drooling, maybe we can support
12 | again your efforts by looking at broader issues. You
13 | mentioned a separate meeting where maybe we just talk about
14 | templates or some of the other issues that come before all
15 | of you that we might help with. It occurs to me that maybe
16 | having somebody from the NICHD -- I don't know if there's
17 | anybody within the NIH like yourself that coordinates all
18 | of these pediatric studies, but if there was or if they
19 | maybe should create one so that we don't duplicate efforts
20 | and do know what everybody is doing, maybe that would be an
21 | appropriate time to have that person come.

22 | But overall, again, I think we would all like
23 | to just say what an incredible job you all have done. It's
24 | just overwhelming. I don't know if you all know that
25 | Dianne is also in charge of bioterrorism and antibiotic

1 resistance, any one of which would take a staff of 50.

2 (Laughter.)

3 DR. MURPHY: And antimicrobial development.

4 Just don't forget that one, too.

5 DR. CHESNEY: And you were in charge when there
6 wasn't enough penicillin or chloramphenicol -- I forget.

7 DR. MURPHY: Drug shortages. That plus
8 pregnancy are also in my office.

9 DR. CHESNEY: Pregnancy and drug shortages as
10 well.

11 So, I guess we're willing to help you in any
12 way that we can, but we all emphasize what a tremendous job
13 you've done. Whatever we can do to help support the
14 congressional hearings next month and then obviously to get
15 FDAMA passed again.

16 For this particular session, I really wanted to
17 thank our speakers tremendously for taking the time in
18 coming and for Dr. Kelsey and Dr. Mathis for finding you
19 and for outlining the issues. It's always so impressive to
20 me how much I don't know. I don't know why that should be
21 impressive, but I've just learned a tremendous amount here
22 today. You all did just a superb job of just presenting
23 the issues and making it all very clear. So, I think it
24 was fun for us.

25 I particularly want to acknowledge Jayne

1 Peterson who puts all of this together, including a seating
2 chart so I always know who is where and deciding to do
3 everything right. So, thank you very much, Jayne.

4 And thank you to all the committee members. We
5 all learned, I hope, so much from each other. And our
6 invaluable consultants.

7 Any other comments?

8 Jayne wanted me to remind you that the handout
9 you got you'll see is the Federal Register of Tuesday,
10 April 24th, which is the Subpart D that just came out
11 today. So, you are the first to see that unless somebody
12 was combing the Web this morning.

13 Thank you very much.

14 (Whereupon, at 12:55 p.m., the subcommittee was
15 adjourned.)

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